



Ruthenium-Catalyzed Decarbonylative Addition Reaction of Anhydrides to Alkynes: A Facile Synthesis of Isocoumarins and α -Pyrone

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Complete List of Authors:	Prakash, Rashmi; CSIR-NEIST, Medicinal chemistry Shekarrao, Kommuri; CSIR-NEIST, Medicinal chemistry Gogoi, Sanjib; CSIR-NEIST, Medicinal chemistry division Boruah, Romesh; North East Institute of Science and Technology, Medicinal Chemistry Division

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ARTICLE TYPE

Ruthenium-Catalyzed Decarbonylative Addition Reaction of Anhydrides to Alkynes: A Facile Synthesis of Isocoumarins and α -Pyrone

Rashmi Prakash, Kommuri Shekarrao, Sanjib Gogoi,* and Romesh C Boruah*

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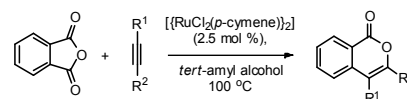
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A novel ruthenium catalyzed straightforward and efficient synthesis of isocoumarin and α -pyrone derivatives has been accomplished by the decarbonylative addition reaction of anhydrides with alkynes under thermal conditions.

Isocoumarins and α -pyrones are the key scaffold of various natural products that show a wide range of exciting biological activities.¹ Some of the α -pyrones exhibit very interesting fluorescence properties^{2a} and they are proved as the bacterial signaling molecules^{2b}.

The transition metal catalyzed decarbonylative addition of anhydrides and alkynes to construct oxygen containing heterocycles is very rare in the literature. The only methodology known so far for such type of tandem reaction of anhydrides and disubstituted alkynes to synthesize biologically important isocoumarins and α -pyrones was reported by Matsubara and coworkers using Ni(cod)₂ (10 mol %) catalyst in the presence of Lewis acid ZnCl₂ (20 mol %) and ligand PMe₃ (40 mol %).³ Herein, we describe that [RuCl₂(*p*-cymene)]₂ (2.5 mol %) alone can catalyze the decarbonylative addition reaction of anhydrides and alkynes to afford good yields of isocoumarins and α -pyrones (Scheme 1). The scope of the Ru catalyzed decarbonylative addition reaction could be enlarged efficiently to wide range of anhydrides and alkynes. It is noteworthy to say that the decarbonylative addition reaction of unsymmetrical anhydrides to disubstituted symmetrical alkynes is very regioselective in this Ru catalyzed reaction.

We started our studies by optimizing reaction conditions for the decarbonylative annulation reaction of anhydride **1a** with toluene **2a** for the synthesis of **3a** (Table 1). At the outset, different metal catalysts were screened as shown in Table 1 and [RuCl₂(*p*-cymene)]₂ turned out to be the optimal catalyst in 1,4-dioxane (entries 1-5). Among a set of representative solvents surveyed for this reaction (entries 6-9), the highest yield (83%) was obtained using *t*-AmOH as the solvent (entry 6). Reactions performed in the presence of commonly used oxidants Cu(OAc)₂, CuBr₂, AgOAc or in presence of additive AgSbF₆, could not further improve the yield of **3a** (not shown in Table 1). With the optimized reaction conditions in hand, we first tested its scope in the decarbonylative annulation reaction of anhydride **1a** with functionalized diaryl-substituted alkynes (**2b-e**). We were delighted to observe that



Scheme 1. Ru catalyzed decarbonylative addition reaction

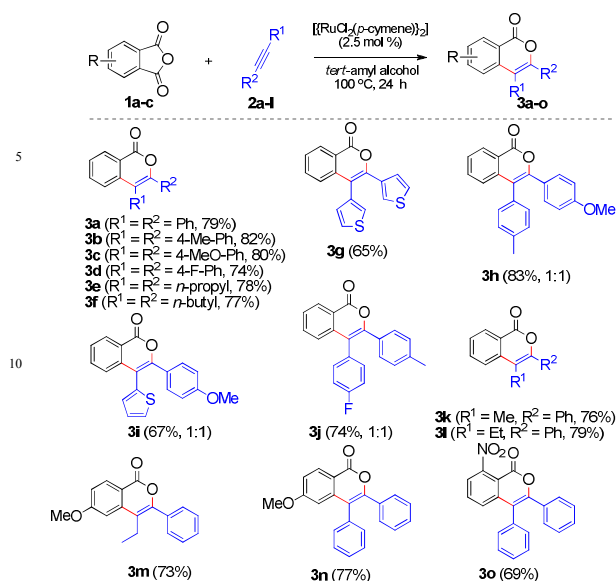
the diaryl-substituted alkynes bearing valuable electron-donating and electron-withdrawing groups in the phenyl ring were well tolerated to provide 74-82% yields of isocoumarins **3b-d**. The dialkyl-substituted alkynes were also found to be suitable substrates to furnish the desired products **3e** and **3f** in 77-78% yields. Moreover, the annulation reaction of alkyne substituted with heterocyclic ring proceeded well to provide corresponding isocoumarin derivative **3g** in 65% yield. The

Table 1. Optimization of the reaction conditions for **3a**^a

entry	catalyst (2.5 mol %)	solvent	3a (%) ^b
1	RuCl ₃ .xH ₂ O	1,4-dioxane	14
2	[RuCl ₂ (PPh ₃) ₃]	1,4-dioxane	19
3	[RuCl ₂ (<i>p</i> -cymene)] ₂	1,4-dioxane	57
4	Pd(OAc) ₂	1,4-dioxane	13
5	[(Cp*RhCl ₂) ₂]	1,4-dioxane	43
6	[RuCl ₂ (<i>p</i> -cymene)] ₂	<i>t</i> -AmOH	83
7	[RuCl ₂ (<i>p</i> -cymene)] ₂	DCE	61
8	[RuCl ₂ (<i>p</i> -cymene)] ₂	DMF	53
9 ^c	[RuCl ₂ (<i>p</i> -cymene)] ₂	<i>t</i> -AmOH	81

^aReaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (2.5 mol %), solvent (3.0 mL), 100 °C, 24 h; unless otherwise mentioned. ^bIsolated yields. ^c5.0 mol % of catalyst.

unsymmetrically substituted alkynes also proved to be good substrates for the decarbonylative annulation reaction and several unsymmetrical alkynes substituted with aryl, heteroaryl and alkyl substituents were reacted with **1a**. The annulation reaction between **1a** and the unsymmetrical alkynes **2h**, **2i** and **2j** afforded a mixture of isocoumarins **3h-j** (~ 1:1) in 67-83% yields. Notably, the annulation reaction between **1a** and the unsymmetrical alkynes **2k** and **2l** were highly regioselective to afford the

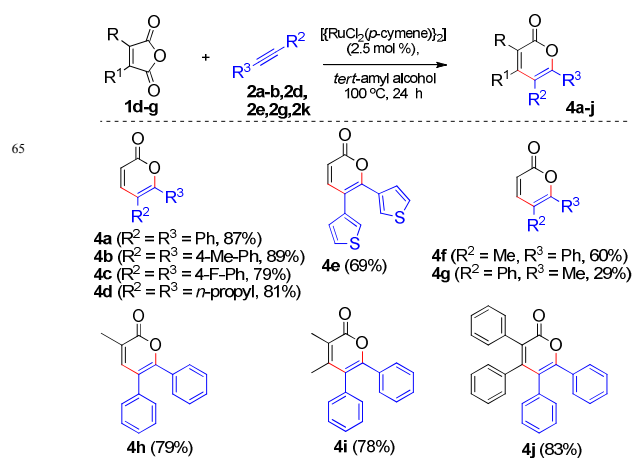
Table 2. Synthesis of various substituted isocoumarins^a

^aReaction conditions: Anhydride (1.0 mmol), alkyne (1.0 mmol) and Ru-catalyst (2.5 mol %) in *tert*-amyl alcohol (3.0 mL) was heated at 100 °C for 24 h under air; Isolated yields.

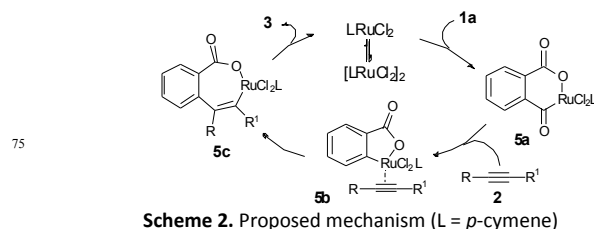
products **3k**⁵ and **3l** in 76–79% yields. Anhydrides, bearing electron-donating or withdrawing groups in the phenyl ring **1b–c**, reacted regioselectively with alkynes **1a** and **1l** to provide the products **3m–o** in good yields (69–77%). The formation of products **3k–m** indicated the initial formation of C–C bond of the phenyl ring carbon with the alkyne carbon bearing the alkyl substituent leading to the formation of the highly regioselective products. The observed alkyne insertion regiochemistry of **3k–m** was similar to the previously reported nickel,^{4a} cobalt^{4b} and palladium^{4c} catalyzed carbocyclization reaction, where insertion of alkyne into carbon–metal bonds occurred with the carbon atom generally attacked the more positive carbon of the alkyne.⁴ Next, the annulation reaction was tested with maleic anhydride **1d**. As shown in Table 3, symmetrical alkynes substituted with aryl, heteroaryl and alkyl substituents, turned out to be better substrates for this annulation reaction and they provided α -pyrones **4a–e** in 69–89% yields under the standard reaction conditions. The reaction of **1d** and unsymmetrical alkyne **2k** provided a easily separable mixture of α -pyrones **4f** and **4g** (**4f**:**4g** = 3:1) in 89% yield. The reaction of unsymmetrical anhydride **1e** and symmetrical alkyne **2a** was highly regioselective under the standard condition to provide α -pyrone **4h**⁵ in 79% yield. In addition, the 3,4-disubstituted maleic anhydrides **1f–g** were converted to pyrones **4i–j** in 78–83% yields. The reaction of **1a** with terminal alkyne *p*-tolylacetylene, under the optimized reaction conditions provided the dimeric product (*Z*)-1,4-di-*p*-tolylbut-1-en-3-yne of the alkyne.⁶ The reaction of **1a** with 2,3-dimethyl-1,3-butadiene or cyclohexylallene, under the optimized reaction conditions provided complex mixture of products. The regioselectivity of the products were proved by comparison of new spectral and physical data with those reported in the literature and from their NOE spectra.⁵

Based on our findings and previous results on ruthenium metal catalyzed functionalization of carbon–oxygen bonds,⁷ as well as on transition metal catalyzed decarbonylative annulation reactions,^{3,8} a plausible mechanism for the formation of **3** is

proposed which is shown in scheme 2. Oxidative addition of ruthenium catalyst to anhydride O–CO bond produces six-membered ruthenium cycle **5a**. Decarbonylation of **5a** and subsequent insertion of alkyne **2** to the C–Ru bond generates seven-membered ruthenium cycle **5c**, which on reductive elimination affords **3** and reinstates the starting Ru catalyst. The improved yield of **3a** in *tert*-amyl alcohol might be due to the electrostatic interaction between ruthenium species (hard acid) with the alcohol (hard base), which increases the stability of the ruthenium complexes.

Table 3. Synthesis of various substituted α -pyrone^a

^aReaction conditions: Anhydride (1.0 mmol), alkyne (1.0 mmol) and Ru-catalyst (2.5 mol %) in *tert*-amyl alcohol (3.0 mL) was heated at 100 °C for 24 h under air; Isolated yields.



In summary, we have described the first example of ruthenium catalyzed decarbonylative addition reaction of anhydrides with alkynes to provide isocoumarins and α -pyrones in high yields. The highly regioselective decarbonylative addition reaction of unsymmetrical anhydrides and disubstituted symmetrical alkynes, broad substrate scope, simple experimental procedure, less catalyst loading and high yield of products are the noteworthy features of this reaction.

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Notes and references

Medicinal Chemistry Division, CSIR-North East Institute of Science and Technology, Jorhat 785006, India, Fax: +913762370011 Tel.: +91 3762372948; skgogoi@gmail.com; rc_boruah@yahoo.co.in

† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, ¹H and ¹³C NMR spectra for new compounds. See DOI:

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