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Ruthenium-catalyzed decarbonylative addition reaction of anhydrides with alkynes: a facile synthesis of isocoumarins and α -pyrones†

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

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 scaffolds 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 to be 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 a 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 the 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 broadened efficiently to a wide range of anhydrides and alkynes. It is noteworthy to say that the decarbonylative addition reaction of unsymmetrical anhydrides

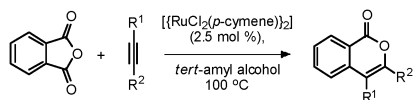
Table 1 Optimization of the reaction conditions for **3a**^a

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	^t 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	^t AmOH	81

^a Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), catalyst (2.5 mol%), solvent (3.0 mL), 100 °C, 24 h, unless otherwise mentioned. ^b Isolated yields. ^c 5.0 mol% of catalyst.

with disubstituted symmetrical alkynes is very regioselective in this Ru catalyzed reaction.

We started our studies by optimizing the reaction conditions for the decarbonylative annulation reaction of anhydride **1a** with tolane **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 ^tAmOH as the solvent (entry 6). The reactions performed in the presence of commonly used oxidants Cu(OAc)₂, CuBr₂, AgOAc or in the presence of the 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 the diaryl-substituted alkynes bearing valuable electron-donating and electron-withdrawing groups in the phenyl ring were well tolerated to provide 74–82% yield of isocoumarins **3b–d**. The dialkyl-substituted alkynes were also found to be suitable substrates to furnish the desired products



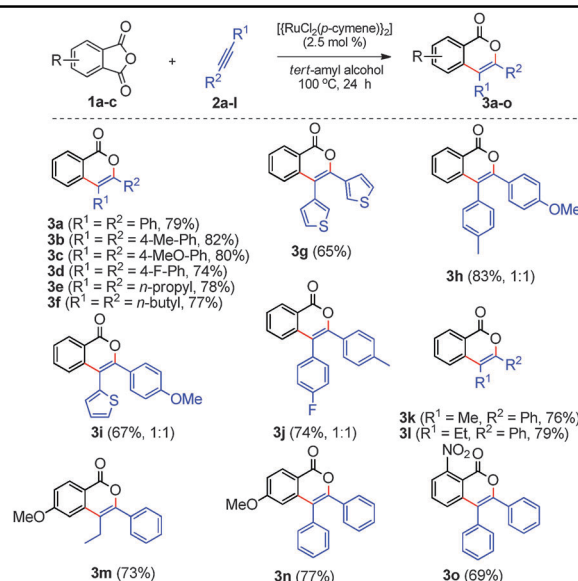
Scheme 1 Ru catalyzed decarbonylative addition reaction.

Medicinal Chemistry Division, CSIR-North East Institute of Science and Technology, Jorhat 785006, India. E-mail: skgogoi1@gmail.com, rc_boruah@yahoo.co.in; Fax: +91 3762370011; Tel: +91 3762372948

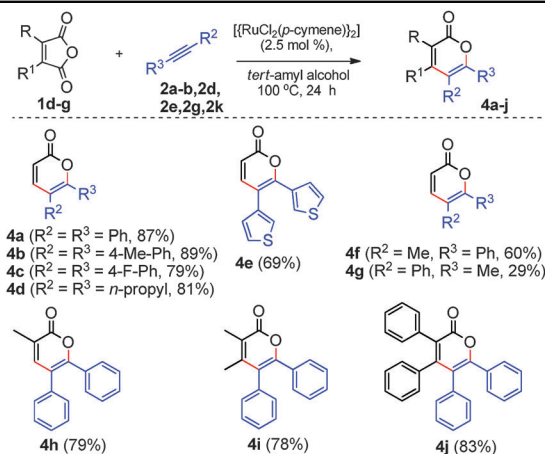
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ¹H and ¹³C NMR spectra of new compounds. See DOI: 10.1039/c5cc03311j

3e and **3f** in 77–78% yield. Moreover, the annulation reaction of the alkyne substituted with a heterocyclic ring proceeded well to provide the corresponding isocoumarin derivative **3g** in 65% yield. The 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% yield. Notably, the annulation reaction between **1a** and the unsymmetrical alkynes **2k** and **2l** was highly regioselective to afford the products **3k**⁵ and **3l** in 76–79% yield. Anhydrides, bearing electron-donating or -withdrawing groups on 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 the 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 the insertion of alkynes into carbon–metal bonds occurred with the carbon atom generally attacking 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% yield under the standard reaction conditions. The reaction of **1d** and unsymmetrical alkyne **2k** provided an 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 conditions 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% yield. 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 a complex mixture of products. The regioselectivity of the products was proved by the comparison of new spectral and physical data with those reported in the literature and from their NOE spectra (Table 2).⁵

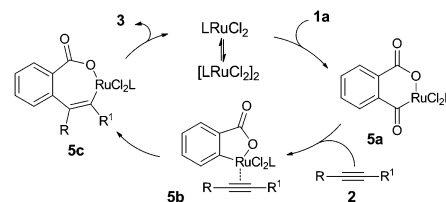
Based on our findings and the previous results on ruthenium metal catalyzed functionalization of carbon–oxygen bonds,⁷ as well as on the transition metal catalyzed decarbonylative annulation reactions,^{3,8} a plausible mechanism for the formation of **3** is proposed, which is shown in Scheme 2. Oxidative addition of the ruthenium catalyst to the 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 the ruthenium species

Table 2 Synthesis of various substituted isocoumarins^a

^a Reaction conditions: anhydride (1.0 mmol), alkyne (1.0 mmol) and the Ru-catalyst (2.5 mol%) in *tert*-amyl alcohol (3.0 mL) were heated at 100 °C for 24 h under air; isolated yields.

Table 3 Synthesis of various substituted α -pyrones^a

^a Reaction conditions: anhydride (1.0 mmol), alkyne (1.0 mmol) and the Ru-catalyst (2.5 mol%) in *tert*-amyl alcohol (3.0 mL) were heated at 100 °C for 24 h under air; isolated yields.

Scheme 2 Proposed mechanism (L = *p*-cymene).

(hard acid) with the alcohol (hard base), which increases the stability of the ruthenium complexes.

In summary, we have described the first example of the 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, a broad substrate scope, simple experimental procedures, low catalyst loading and high yield of products are the noteworthy features of this reaction.

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