Ruthenium-Catalyzed Regioselective Reactions of Nitriles and 1,3-Dicarbonyl Compounds with Terminal Alkynes¹

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Received 23 September 2009

Abstract: $\text{RuH}_2(\text{PPh}_3)_4$ -catalyzed reaction of nitriles with terminal alkynes proceeds highly efficiently under neutral conditions to give the corresponding Michael adducts. Furthermore, 1,3-dicarbonyl compounds react with terminal alkynes at the α -position to afford the *exo*-methylene compounds with high regioselectivity under neutral conditions. The regioselectivity depends upon the change of substrates. The precise mechanism is presented.

Key words: ruthenium catalyst, regioselective addition, nitriles, 1,3-dicarbonyl compounds, alkynes

The activation of α -C–H bond adjacent to heteroatoms by α -heteroatom effect leads to find a series of catalytic methods for selective carbon–carbon bond formation.² Transiton-metal polyhydride complexes such as RuH₂(PPh₃)₄ and IrH₅(Pi-Pr)₂ are excellent catalysts for the activation of α -C–H bond of various substrates. The reactions of nitriles,³ isocyanates,⁴ trifluoromethylated compounds,⁵ and carbonyl compounds⁶ with electrophiles proceed catalytically under neutral conditions highly efficiently.



Equation 1



Equation 2

We wish to report that ruthenium-catalyzed reactions of nitriles with alkynes bearing electron-withdrawing substituents give the corresponding adducts highly efficiently (Equation 1) and that similar ruthenium-catalyzed reactions of 1,3-dicarbonyl compounds with alkynes give *exo*methylene compounds regioselectively (Equation 2).

SYNLETT 2009, No. 20, pp 3355–3359 Advanced online publication: 18.11.2009 DOI: 10.1055/s-0029-1218373; Art ID: U09709ST © Georg Thieme Verlag Stuttgart · New York Concerning the latter reaction highly useful regioselective addition of 1,3-dicarbonyl compounds to terminal alkynes have been reported using indium,⁷ gold,⁸ rhenium,⁹ and nickel¹⁰ catalysts. The present ruthenium-catalyzed reaction is compatible to these reactions.

The catalytic activity of various metal complexes was examined with respect to the reaction of ethyl 2-cycanopropanoate (2) with methyl propiolate (3) in dry THF at room temperature for five minutes. $\text{RuH}_2(\text{PPh}_3)_4$ (1) gave the best result for the formation of 2-cyano-2-methyl-3-pentenedioate (4). The other transition-metal catalysts such as $\text{RhH}(\text{PPh}_3)_4$, $\text{RhH}(\text{CO})(\text{PPh}_3)_3$, $\text{IrH}(\text{CO})(\text{PPh}_3)_3$, and $\text{Pd}(\text{PPh}_3)_4$ gave satisfactory results.

Representative results of the reactions of nitriles with terminal alkynes in the presence of the catalyst 1 are shown in Table 1. Interestingly, the regioselectivity of the reaction of nitriles to alkynes changes dramatically depending on the structure of nitriles. We obtained a contrast result depending on the presence of α -substituent of nitriles. The ruthenium-catalyzed reactions of α -disubstituted acetonitriles with terminal alkynes gave the products 6-10 as shown in Table 1. The ratios of the Z- and E-isomers are also listed in Table I. Typically, the reaction of α -methylsubstituted pivaloyl acetonitrile (11) with methyl propiolate 3 in the presence of the catalyst 1 gave methyl 4cyano-4,6,6-trimethyl-5-oxo-2-heptenoate (12) in 82% yield. In contrast, the reaction of pivaloyl acetonitrile (13) that has no substituent at the α -position with **3** gave a mixture of methyl 3-cyano-5,5-dimethyl-2-methylene-4-oxohexanoate (14) and methyl (2Z)-3-cyano-2,5,5-trimethyl-4-oxo-2-hexanoate (15) in 78% yield exclusively. Both compounds were derived from the α -attack to the carbon-



Scheme 1

carbon triple bond of the alkyne. The ratio of the product **14/15** is 4:96. The structure of **15** was determined by NOESY. Under the reaction conditions the product **14** underwent isomerization to give the product **15**. In this reaction the product derived from the β -attack could not be detected. The compounds **14** would be derived from the α -attack of alkyne, and then subsequent isomerization of **14** under the reaction conditions would give the product **15**.

These reactions can be rationalized by assuming the mechanism shown in Scheme 1. We have found that the C-bonded ruthenium complex 16, which derived from the C–H activation α to nitrile by heteroatom effect, under-

goes isomerization to give the N-bonded ruthenium complex 17.¹¹ The structures of these two complexes are dependent on the cone angle of the phosphine ligands. The phosphine bearing larger cone angle forms N-bonded complexes, while phosphine with smaller cone angle forms the C-bonded complex because of steric effect. In the reaction, the N-bonded complex 17 undergoes reaction with terminal alkynes at the β -position to give the Michael-type addition products 6–10 and 12. In contrast, nitriles bearing no α -substituent undergo addition reaction via the C-bonded complex 16. Addition of the ruthenium hydride of 16 to alkynes gives the opposite orientation of the addition as shown in Scheme 1.

Table 1 Ruthenium-Catalyzed Reaction of Nitriles with Alkynes^a

Entry	Nitrile	Alkyne	Product	Yield $(\%)^{b}(Z/E)$
1	NC CO ₂ Et	CO ₂ Me 3	EtO ₂ C Me NC CO ₂ Me	94 (59:41)
2	Me NC CO2Et	──C(O)Me 5	EtO ₂ C Me NC	81 (76) ^c (65:35)
3	NC CO ₂ Et	──C(O)Me	EtO ₂ C Ph NC	82 ^d (35:65)
4	Me NC Ph	──C(O)Me	Me NC 8	54 (69:31)
5	NC Ph	──C(O)Me	Me NC NC 9	79 (56:44)
6	NC Ph		Me NC	71 (95:5)
7	NC t-Bu	──CO ₂ Me 3	t-Bu(O)C Me NC NC NC NC NC	82 (45:55)
	11		t-Bu(O)C	
8	NC t-Bu O 13	──CO ₂ Me	14 t-Bu(O)C NC	78 (14/15 = 4:96)
			CO ₂ Me	

^a A mixture of nitrile (2.0 mmol), alkyne (2.2 mmol), and catalyst 1 (0.06 mmol) in dry THF (0.5 mL) was stirred at r.t. for 24 h under argon.

^b Isolated yield based on the nitrile. The *E*/*Z* ratio of the product, determined by ¹H NMR analysis, was shown in parenthesis.

^c Pd(PPh₃)₄ catalyst was used instead 1.

^d RhH(PPh₃)₄ (0.06 mol) was used instead of **1**.

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Similar regioselectivity was observed for the rutheniumcatalyzed reaction of 1,3-dicarbonyl compounds with alkynes. 1,3-Dicarbonyl compounds attack at the α -position of alkynes with high regioselectivity to afford the corresponding *exo*-methylene compounds (Equation 2). Typically, the reaction of acetylacetone with 3-butyn-2one in the presence of RuH₂(PPh₃)₄ catalyst in dry THF in a sealed tube at 80 °C for one hour, 3-acetyl-4-methylene-2,5-hexanedione (**18**) was obtained in 71% yield. The keto/enol ratio is 9:91.

Representative results of the ruthenium-catalyzed reaction of 1,3-dicarbonyl compounds bearing no substituent at the α -position with alkynes are summarized in Table 2. Various 1,3-dicarbonyl compounds such as 1,3-diketones, β -keto esters, and β -keto amides underwent the reaction with various alkynes at the α -positions selectively. No adduct derived from the β -attack was observed. RuH₂(PPh₃)₄ and IrH(CO)(PPh₃)₃ have proved to be effective catalysts. Other transition-metal hydride complexes, such as RuH₂(CO)(PPh₃)₃, RhH(PPh₃)₄, RhH(CO)(PPh₃)₃, and Pd(PPh₃)₄ also showed high catalytic activity.

 Table 2
 Ruthenium-Catalyzed Addition of 1,3-Dicarbonyl Compounds to Alkynes^a

Entry	1,3-Dicarbonyl Compound	Alkyne	Product	Yield (%) ^b	Keto/enol
1	Me Me	——C(O)Me	Me(O)C Me(O)C C(O)Me	71	9:91
2	Me Me	──CO ₂ Me	18 Me(O)C Me(O)C CO ₂ Me	73 (83)°	6:94
3	Me Me		19 Me(O)C MeOC O O	79	8:92
4	Me Me	OEt	20 Me(O)C MeOC OEt	86	7:93
5	PhMe OO	C(O)Me	C(O)Me C(O)Me	70 ^d	72:28
6	Me	──CO ₂ Me	C(O)Me	90	34:66
7	Me NH ₂	──CO ₂ Me	$H_2 NOC + CO_2 Me$	53 ^d	52:48
8	Me OMe	──CO ₂ Me	C(O)Me MeO ₂ C CO_2Me	55°	56:44

Entry

9

10

Table 2 Ruthenium-Catalyzed Addition of 1,3-Dicarbonyl Compounds to Alkynes^a (continued)

-C(O)Me

Мe

C(O)Me

Me Ċ(O)Me

27

Me

28

C(O)Me

^a A mixture of 1,3-dicarbonyl compound (1.0 mmol), alkyne (2.0 mmol), and catalyst 1 (0.03 mmol) in dry THF (2.0 mL) was heated at 80 °C for 1 h under argon.

^b Isolated yield based on the 1.3-dicarbonyl compound.

- ^c IrH(CO)(PPH₃)₄ (0.03 mmol) was used instead of 1.
- ^d Reaction time 12 h.
- ^e Reaction temperature: 60 °C.

The products are sensitive even to column chromatography. The products obtained are mixtures of keto and enol isomers. This was confirmed by ¹H NMR and ¹³C NMR analyses and DEPT. The ratios of the keto/enol are also shown in Table 2.

The reaction can be rationalized by assuming the mechanism shown in Scheme 2.

Insertion of low-valent ruthenium species to the α -C-H bond of 1,3-dicarbonyl compounds would give the ruthenium hydride intermediate 29, which undergoes isomerization to the hydrido(enolate)ruthenium intermediate 30. Insertion of ruthenium hydride species of 29 to alkynes would give the intermediate 31, and subsequent reductive elimination of the ruthenium species would give the product 32. To confirm this, the reaction of Ru(ethylene)(PPh₃)₃ with acetyl acetone was carried out, and the complex 35 was obtained. The reaction of acetyl acetone with methyl propiolate in the presence of catalyst 35 gave methyl 3-acetyl-2-methylene-4-oxopentanoate (19) in

51







Scheme 2

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27/

28 = 70:30



Equation 4

74% yield (Equation 3). In addition, we investigated the reaction of acetyl acetone with deuterated methyl propiolate (94% deuterated). The result of the deuterium distribution is shown in Equation 4. This may be due to the addition–elimination of the ruthenium hydride species to the product **19**.

It is noteworthy that the contrast regioselectivity was obtained for the reactions of α -substituted 1,3-dicarbonyl compounds with alkynes likewise the reaction of nitriles as above mentioned. Thus, the reaction of 3-methyl-2,5pentanedione with 3-butyn-2-one in the presence of catalyst 1 in THF in a sealed tube at 80 °C gave a mixture of 3-acetyl-3-methyl-4-heptene-2,6-dione (27) and 3-acetyl-3-methyl-4-methylenehexane-2,5-dione (28; 27/28 = 70:30) in 51% yield. In this reaction the reaction of the carbon nucleophile of 30 to the β -position of the alkyne would give the intermediate 33, which undergoes reductive elimination of ruthenium species to give the product 34.

The contrast regioselectivity observed in the reactions of nitriles and 1,3-dicarbonyl compounds with terminal alkyne depends on the change in substrate structure at the α -position. This is due to the structure of the intermediate derived from the C–H activation of the substrates. It is noteworthy that low-valent ruthenium catalyst RuH₂(PPh₃)₄ plays an important role, which may correspond to Lewis acid catalysts such as indium catalysts.⁷ Work is in progress to determine the structure of the reactive ruthenium species and to apply this new catalytic system to the other reactions.

Acknowledgment

This work was supported by a Grant-in-Aid for Scientific Research, the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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