ORGANIC LETTERS

2007
Vol. 9, No. 24
5111−5114

Copper/Silver-Cocatalyzed Conia-Ene Reaction of Linear β-Alkynic β-Ketoesters

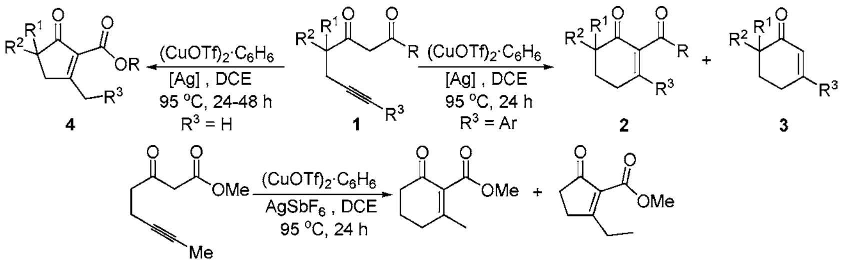
Chen-Liang Deng, Ren-Jie Song, Sheng-Mei Guo, Zhi-Qiang Wang, and Jin-Heng Li*

Key Laboratory of Chemical Biology & Traditional Chinese Medicine Research (Ministry of Education), Hunan Normal University, Changsha 410081, China

jhli@hunnu.edu.cn

Received September 25, 2007

ABSTRACT



A novel and general copper/silver catalytic system has been developed for the Conia-ene intramolecular reaction of linear β-alkynic β-ketoesters. In the presence of $(CuOTf)_2 \cdot C_6H_6$ and $AgSbF_6$ (or AgOAc), a variety of the linear β-alkynic β-ketoesters selectively underwent the Conia-ene intramolecular reaction in moderate to good yields.

The intramolecular ene reaction of unsaturated ketones and aldehydes, namely, the Conia-ene reaction, is an important method for the formation of carbon−carbon bonds.[1−7] There are two common transformations, one involving thermal cyclization[2] and the other transition-metal-catalyzed cyclization (eq 1).[3−7] However, the application of the former in organic synthesis is limited because of the requirement of high temperature. Although the latter transformation could be conducted smoothly at lower temperature, additives such as strong base,[3] strong acid,[4] and photochemical activation (often UV irradiation) are often needed.[5] Balme and co-

---

(1) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, pp 1−63.

(2) For a review, see: Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1.

(3) Pd: (a) Fournet, G.; Balme, G.; Van, Hemelryck, B.; Gore, J. *Tetrahedron Lett.* **1990**, *31*, 5147. (b) Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1991**, *47*, 6293. (c) Bouyssi, D.; Balme, G.; Gore, J. *Tetrahedron Lett.* **1991**, *32*, 6541. (d) Balme, G.; Bouyssi, D.; Faure, R.; Gore, J.; Van Hemelryck, B. *Tetrahedron* **1992**, *48*, 3891. (e) Monteiro, N.; Gore, J.; Balme, G. *Tetrahedron* **1992**, *48*, 10103. Mo: (f) McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691. Cu: (g) Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297. (h) Perez-Hernandez, N.; Febles, M.; Perez, C.; Perez, R.; Rodriguez, M. L.; Foces-Foces, C.; Martin, J. D. *J. Org. Chem.* **2006**, *71*, 1139. Ti: (i) Kitagawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470.

(4) (a) Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801. (b) Boaventura, M. A.; Drouin, J. *Synth. Commun.* **1987**, *17*, 975. (c) Cruciani, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1994**, *35*, 6677. (d) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699. (e) Renaud, J.-L.; Petit, M.; Aubert, C.; Malacria, M. *Synlett* **1997**, 931. (f) Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113. (g) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168.

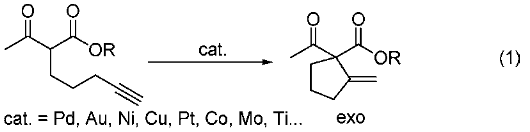
(5) (a) Stammler, R.; Malacria, M. *Synlett* **1994**, 92. (b) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699. (c) Renaud, J.-L.; Aubert, C.; Malacria, M. *Tetrahedron* **1999**, *55*, 5113.

(6) Au: (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350. (c) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133. (d) Atsuko, O.; Hideto, I.; Masaya, S. *J. Am. Chem. Soc.* **2006**, *128*, 16486. (e) Pan, J.-H.; Yang, M.; Gao, Q.; Zhu, N.-Y.; Yang, D. *Synthesis* **2007**, 2539. Ni: (f) Gao, Q.; Zheng, B.-F.; Li, J.-H.; Yang, D. *Org. Lett.* **2005**, *7*, 2185.

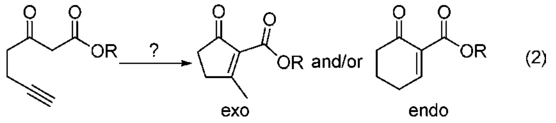
(7) (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002. (b) Nakamura, M.; Endo, K.; Nakamura, E. *Org. Lett.* **2005**, *7*, 3279. (c) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823. (d) Nishimura, Y.; Ameniya, R.; Yamaguchi, M. *Tetrahedron Lett.* **2006**, *47*, 1839. (e) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264.

10.1021/ol7023289 CCC: $37.00

workers, for example, have reported that the Conia-ene reactions of α-alkynic β-ketoesters could be conducted smoothly in moderate to excellent yields using CuI as the catalyst. However, a strong base, *tert*-BuOK, was necessary to improve the reaction. Consequently, much recent attention has focused on the development of mild and neutral conditions for the Conia-ene reaction.[6] Toste, for instance, reported a mild and efficient $(PPh_3)AuCl/AgOTf$-catalyzed Conia-ene intramolecular reaction of α-alkynic β-ketoesters in good yields.[6a] Recently, Yang also developed a mild and effective protocol for the Conia-ene reactions of α-alkynic β-ketoesters using the $Ni(acac)_2/Yb(OTf)_3$ catalytic system.[6d] Unfortunately, almost all of these catalytic protocols are focused on the reactions of α-alkynic β-ketoesters, and a linear β-alkynic β-ketoester was only employed as substrate in the $[Au(N(SO_2CF_3)_2(triethynyphosphine)]$-catalyzed Conia-ene reaction to afford an *exo*-product in quantitative yield.[6c] Thus, the development of an inexpensive and general catalytic system for the Conia-ene reactions of the linear β-alkynic β-ketoesters under neutral conditions is still interesting (eq 2). Herein, we wish to report a Cu(I)/Ag catalytic system for the Conia-ene reactions of the linear β-alkynic β-ketoesters in moderate to good yields.[3g,h]



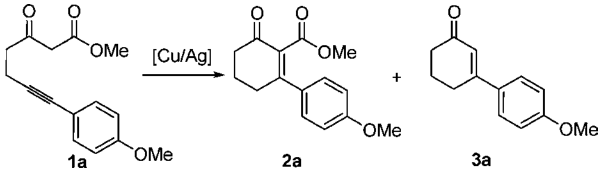
(1)



(2)

As listed in Table 1, methyl 7-(4-methoxyphenyl)-3-oxohept-6-ynoate (**1a**), a linear β-alkynic β-ketoester, was chosen as a model substrate to screen the optimal reaction conditions.[8] No reaction was observed using CuI, CuI/*tert*-BuOK (Balme's conditions[3g]), or CuI/AgOTf catalytic system (entries 1−3). To our delight, an *endo*-product **2a** was isolated in a 8% yield using $(CuOTf)_2{\cdot}C_6H_6$ as the catalyst (entry 4). Interestingly, AgOAc also provided the target product **2a** in a 24% yield (entry 5). These prompted us to examine the Cu/Ag cocatalysts' effect on the reaction. In the presence of $(CuOTf)_2{\cdot}C_6H_6$, a number of silver salts, including AgOTf, AgOAc, $AgSbF_6$, $AgBF_4$, $AgNO_3$, Ag_2O, and Ag_2CO_3, were first tested. The results indicated that AgOAc, $AgSbF_6$, or $AgBF_4$ gave the better results.[6] A 67% yield of **2a** was achieved from the reaction of substrate **1a** catalyzed by $(CuOTf)_2{\cdot}C_6H_6$ combined with AgOAc (entry 6). Identical results were also obtained using $(CuOTf)_2{\cdot}C_6H_6/AgBF_4$ cocatalysts (entry 7). Surprisingly, the Conia-ene cyclization/decarboxylation sequence occurred in the reaction substrate **1a** with $(CuOTf)_2{\cdot}C_6H_6$ and AgOTf to afford a decarboxylated *endo*-product **3a** alone in a 26% yield (entry 8).[9] Interestingly, $AgSbF_6$ combined with $(CuOTf)_2{\cdot}C_6H_6$ provided a 92% total yield involving a 61% yield of **2a** and a 31% yield of **3a** (entry 9). Although in the presence of $(CuOTf)_2{\cdot}C_6H_6$ and $AgSbF_6$ the product **2a** could be obtained alone at 50 °C, the yield was reduced to some extent even with prolonging the time (entry 10). Finally, attempts to enhance the yield of the decarboxylated product **3a** by increasing the temperature were successful, and the product **3a** was obtained exclusively in a 57% yield at 155 °C (entry 11).[9]

Table 1. Screening Conditions for the Conia-Ene Reaction[a]



entry	[Cu]	[Ag]	isolated yield (%) 2a	3a
1	CuI	−	trace	trace
2[b]	CuI	−	trace	trace
3	CuI	AgOTf	<5	trace
4	$(CuOTf)_2{\cdot}C_6H_6$	−	8	trace
5	−	AgOAc	24	trace
6	*$(CuOTf)_2{\cdot}C_6H_6$*	*AgOAc*	*67*	*trace*
7	$(CuOTf)_2{\cdot}C_6H_6$	$AgBF_4$	62	trace
8	$(CuOTf)_2{\cdot}C_6H_6$	AgOTf	trace	26
9	*$(CuOTf)_2{\cdot}C_6H_6$*	*$AgSbF_6$*	*61*	*31*
10[c]	$(CuOTf)_2{\cdot}C_6H_6$	$AgSbF_6$	56	0
11[d]	$(CuOTf)_2{\cdot}C_6H_6$	$AgSbF_6$	trace	57

[a] Reaction conditions: **1a** (0.2 mmol), [Cu] (10 mol %) and [Ag] (10 mol %) at 95 °C in CH_2ClCH_2Cl (DCE; 5 mL) under argon atmosphere for 23 h. [b] *tert*-BuOK (15 mol %) in THF (5 mL) at 30 °C for 4 h then 95 °C for 24 h. [c] At 50 °C for 46 h. [d] At 155 °C for 46 h.

With the standard reaction conditions in hand, a variety of linear β-arylacetylenic β-ketoesters were surveyed to investigate scope (Table 2). The results demonstrated that only *endo*-products were observed, but the yield and selectivity were affected by the structures of β-ketoesters. Substrates **1b**−**d** bearing electron-rich or electron-neutral aryl groups at the terminal of alkyne, for instance, were treated with $(CuOTf)_2{\cdot}C_6H_6$ and $AgSbF_6$ smoothly to afford the corresponding *endo*-products in good total yields (entries 1−4). However, substrate **1e** having an electron-deficient group at the terminal of alkyne gave a low yield together with another byproduct (entry 5).[10] Subsequently, the groups of ester were tested under the standard conditions, and methyl, ethyl, or isopropyl was tolerated well (entry 9 in Table 1 and entries 6 and 8 in Table 2). Isopropyl ester (**1g**), for instance, was treated with $(CuOTf)_2{\cdot}C_6H_6$ and $AgSbF_6$ smoothly at 95 °C in a 69% total yield. Interestingly, the reactions of the hindered 4-substituted 3-ketoesters **1h** and

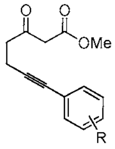
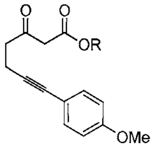
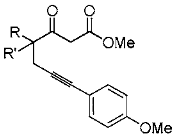
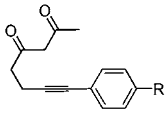
---

(8) For detailed experimental data, see Table S1 in Supporting Information.

(9) The decarboxylated products are readily observed in the presence of transition-metal catalyst under higher reaction temperature conditions; see: (a) Yamamoto, A. *Adv. Organomet. Chem.* **1992**, *34*, 111. (b) Lin, Y.-S.; Yamamoto, A. In *Activation of Unreactive Bonds and Organic Synthesis*; Murai, S., Ed.; Springer: Berlin, Germany, 1999; pp 161−192.

(10) See eq S1 in Supporting Information.

Table 2. Cu/Ag-Cocatalyzed Conia-Ene Reaction[a]

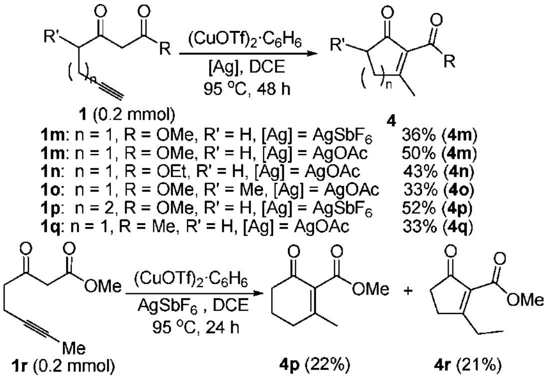
entry	dicarbonyl		time (h)	yield (%)[b] 2	3
1		R = 2-MeO (**1b**)	48	26 (**2b**)	23 (**3b**)
2		R = 4-Me (**1c**)	46	49 (**2c**)	27 (**3c**)
3[c]		(**1c**)	46	0 (**2c**)	52 (**3c**)
4		R = H (**1d**)	45	51 (**2d**)	35 (**3d**)
5[d]		R = 4-MeCO (**1e**)	48	17 (**2e**)	0 (**3e**)
6		R = Et (**1f**)	46	52 (**2f**)	16 (**3a**)
7[c]		(**1f**)	46	0 (**2f**)	45 (**3a**)
8		R = *i*-Pr (**1g**)	48	35 (**2g**)	34 (**3a**)
9[c]		(**1g**)	48	0 (**2g**)	48 (**3a**)
10		R = Me, R′ = H (**1h**)	21	68 (**2h**)	0 (**3h**)
11[e]		(**1h**)	21	54 (**2h**)	0 (**3h**)
12		R = R′ = Me (**1i**)	22	49 (**2i**)	0 (**3i**)
13		R = 4-MeO (**1j**)	36	44 (**2j**)	33 (**3a**)
14		R = 4-Me (**1k**)	36	17 (**2k**)	17 (**3c**)
15		R = H (**1l**)	36	35 (**2l**)	26 (**3d**)

[a] Reaction conditions: **1** (0.2 mmol), $(CuOTf)_2{\cdot}C_6H_6$ (10 mol %), $AgSbF_6$ (10 mol %), at 95 °C in DCE (5 mL) under argon atmosphere. [b] Isolated yield. [c] At 155 °C. [d] See eq S1 in Supporting Information. A byproduct **5e** was isolated in 30% yield. [e] AgOAc (10 mol %) instead of $AgSbF_6$.

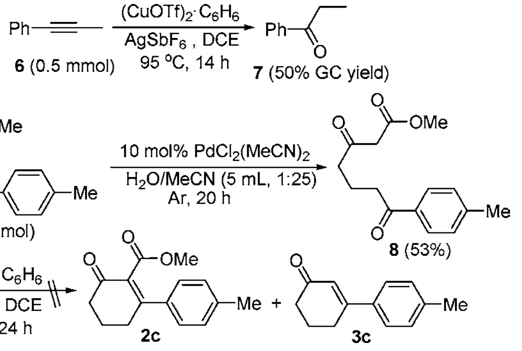
1i selectively afforded the desired products **2h** and **2i** exclusively in moderate yields (entries 10−12). We were happy to find that 3-arylacetylenic 1,3-diketos **1j**−**l** were also suitable substrates under the standard conditions (entries 13−15). Note that the decarboxylated products **3** can still be obtained alone in moderate yields at 155 °C (entries 3, 7, and 9). Unfortunately, no target product was observed from the reaction of methyl 7-(4-methoxyphenyl)-2-methyl-3-oxohept-6-ynoate, a substrate bearing a methyl group at the α-position.

The reactions of terminal alkynes **1m**−**q** or a middle alkylalkyne **1r** were conducted under the standard conditions, and the results are summarized in Scheme 1. In the presence of $(CuOTf)_2{\cdot}C_6H_6$ and silver salt ($AgSbF_6$ or AgOAc), a number of terminal alkynes **1m**−**q** underwent the Conia-ene cyclizations successfully to selectively generate the corresponding *exo*-products **4m**−**q** alone in 33−53% yields. Interestingly, alkyne **1r**, a substrate bearing a methyl group at the terminal of alkyne, gave a mixture of the *endo*-product **4q** and *exo*-product **4r** in 22 and 21% yields, respectively.

Scheme 1. The Conia-Ene Cyclizations of Substrates **1m**−**r**



Scheme 2. Some Controlled Reactions



To elucidate the mechanism of the present protocol, some controlled reactions were conducted as shown in Scheme 2. 1-Phenylpropyne (**6**) was hydrated readily by $(CuOTf)_2{\cdot}C_6H_6$ and $AgSbF_6$ to afford propiophenone (**7**) in a 50% yield, which was determined by GC−MS analysis. The results implied that the present protocol may proceed via the alkyne hydration followed by Knovenagel condensation process.[11] To verify it, substrate **1c** was first hydrated to give methyl 3,7-dioxo-7-*p*-tolylheptanoate (**8**) in the presence of $PdCl_2(MeCN)_2$.[12] Subsequently, the compound **8** was treated with $(CuOTf)_2{\cdot}C_6H_6$ and $AgSbF_6$ at 95 °C for 24 h; however, no target products **2c** and **3c** were observed by GC−MS analysis. On the other hand, a hydrated decarboxylated product **5e**, not the decarboxylated cyclization products **3e**, was isolated from the reaction of alkyne **1e** (entry 5 in Table 2). All the results demonstrated that there was competition between the Conia-ene cyclization reaction and the hydration reaction.

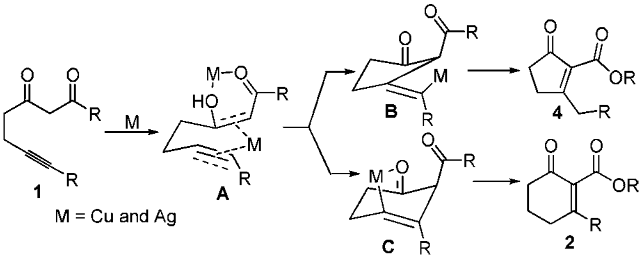
Thus, another working mechanism as outlined in Scheme 3 was proposed on the basis of the previously reported mechanism.[1−7] During the Conia-ene reaction of α-alkynic *β*-ketoesters, two mechanisms were proposed: (1) nucleophilic attack on a M-alkyne complex by the enol form of the ketoester, and (2) a M-enolate formation by directly complexing it with the *β*-ketoester, followed by a *cis*-carbonmetalation of the alkyne.[6] The present results suggested that intermediate **A** may be generated by the complex of one metal with alkyne and another metal with *β*-ketoester,

---

[11] (a) Chang, H.-K.; Datta, S.; Das, A.; Odedra, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4744. (b) Chang, H.-K.; Liao, Y.-C.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 8139.

[12] Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127.

Scheme 3. A Working Mechanism



which is similar to the mechanism proposed by Toste.[6] The intramolecular attack of the M-enolate on the M-alkyne complex then occurred to form intermediates **B** and **C**, followed by a protonation/isomerization sequence to give the corresponding *endo*- or *exo*-products. The present results showed that the selectivity toward *endo*- or *exo*-products depended on the substitutes at the terminal of alkynes. On the basis of the previous and present results,[1−7] we deduced that the *endo*-products were obtained exclusively from γ-arylacetylenic β-ketoesters due to the properties, such as steric hindrance, of the aryl group at the terminal alkyne.

In summary, we have developed a novel copper/silver-cocatalyzed Conia-ene intramolecular reaction of the linear β-alkynic β-ketoesters. In the presence of $(CuOTf)_2 \cdot C_6H_6$ and $AgSbF_6$ (or AgOAc), a variety of the linear β-alkynic β-ketoesters selectively underwent the Conia-ene intramolecular reaction in moderate to good yields. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently underway.

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20572020), New Century Excellent Talents in University (No. NCET-06-0711), Specialized Research Fund for the Doctoral Program of Higher Education (No. 20060542007), Fok Ying Tung Education Foundation (No. 101012), and the Key Project of Chinese Ministry of Education (No. 206102) for financial support. We also thank Professor Dan Yang (The University of Hong Kong) for helpful discussions.

Supporting Information Available: Analytical data and spectra (^{1}H and ^{13}C NMR) for all the products **2−5**; typical procedure for the copper/silver-cocatalyzed Conia-ene intramolecular reaction of the linear γ-alkynic β-ketoesters. This material is available free of charge via the Internet at http://pubs.acs.org.

OL7023289