JOC*Note*

# Ruthenium-Catalyzed Oxidative Cleavage of Alkynes to Carboxylic Acids

Dan Yang,*[†,‡] Fei Chen,[†] Ze-Min Dong,[†] and Dan-Wei Zhang[‡]

*Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, China, and Department of Chemistry, Fudan University, Shanghai 200433, China*

*yangdan@hku.hk*

*Received December 7, 2003*

**Abstract:** We describe an efficient method for the oxidative cleavage of alkynes to carboxylic acids using a combination of $RuO_2$/Oxone/$NaHCO_3$ in a $CH_3CN/H_2O$/EtOAc solvent system. Both internal and terminal alkynes, regardless of their electron density, can be oxidized to carboxylic acids in excellent yield (up to 99%). $^1H$ NMR spectroscopy and ESI-MS experiments provided evidence for α-diketones and anhydrides as possible intermediates in these oxidation reactions.

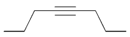
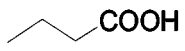
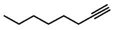
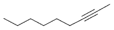
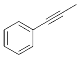
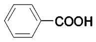
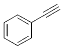
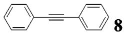
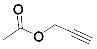
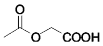
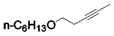
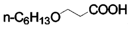
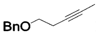
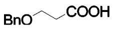
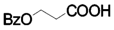
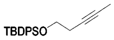
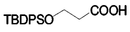
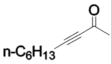
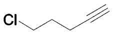
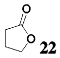
The oxidative cleavage of alkynes to carboxylic acids is a fundamental class of reactions in organic chemistry. Available methods employ oxidants such as ozone,[1] potassium permanganate,[2] ruthenium tetraoxide,[3] Mo and W polyoxometalates,[4] methylrhenium trioxide,[5] alkaline hydrogen peroxide,[6] and [bis(trifluoroacetoxy)iodo]benzene.[7] However, most of these methods are not efficient enough to be utilized for synthetic purposes. For example, ozonolysis is used commonly for the cleavage of both terminal and internal alkynes, but a special apparatus is needed to prevent any possible explosion, and potentially unwanted esters are obtained as side products when the reaction is conducted in alcohol solutions.[1b] Other oxidation methods usually form α-diketones as the main side products, and their further cleavage to carboxylic acids is difficult to achieve under the oxidation conditions described above. Lewis acids[2c] and ultrasound[2b] can promote the oxidative cleavage of alkynes by potassium permanganate, but successful examples of the use of this approach are limited. Griffith et al.[3c] have found that periodic acid can oxidize terminal alkynes to carboxylic acids in the presence of a catalytic amount of $RuCl_3$ in a $H_2O/CCl_4/CH_3CN$ solvent system, but no examples were reported in which internal alkynes were applied as substrates. We found that internal alkynes were tricky to be oxidized to carboxylic acids in such a system because the α-diketone intermediates were difficult to cleave. Therefore, there is high demand for a general and efficient method for the oxidative cleavage of alkynes to carboxylic acids.

**SCHEME 1**

$$\underset{\mathbf{1}}{n\text{-}C_6H_{13}\!-\!\!\equiv\!\!-\!C_6H_{13}\text{-}n}\ \xrightarrow[\text{CH}_3\text{CN/H}_2\text{O/EtOAc (15:10:3), rt, 1h}]{\text{RuO}_2\text{ (3 mol \%), Oxone (3.3 equiv), NaHCO}_3\text{ (9.9 equiv)}}\ \underset{\mathbf{2}}{n\text{-}C_6H_{13}COOH}$$

99%

**TABLE 1. Oxidative Cleavage of Various Alkynes**[a]

| entry | substrate | product | Oxone® equiv. | time (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | **1** | **2** | 3.3 | 1 | 99 |
| 2[c] | **1** | **2** | 3.3 | 1 | 92 |
| 3[d] | **1** | **2** | 3.3 | 1 | 51[e] |
| 4[f] | **1** | **2** | 3.3 | 1 | 99 |
| 5 |  **3** |  **15** | 3.3 | 1 | 80 |
| 6 |  **4** | **2** | 3.3 | 1 | 98 |
| 7 |  **5** | **2** | 3.3 | 1 | 99 |
| 8 |  **6** |  **16** | 4 | 1 | 99 |
| 9 |  **7** | **16** | 4 | 1 | 77 |
| 10 |  **8** | **16** | 4 | 2 | 83 |
| 11 |  **9** |  **17** | 3.3 | 1 | 98 |
| 12 |  **10** |  **18** | 3.3 | 1 | 99 |
| 13 |  **11** |  **19**<br> **20** | 3.5 | 1 | 83[e]<br>14[e] |
| 14 |  **12** |  **21** | 4 | 2 | 99 |
| 15[g] |  **13** | **2** | 6 | 1.5 | 94[e] |
| 16 |  **14** |  **22** | 3.3 | 3 | 74[h] |

[a] Unless otherwise indicated, the reaction was carried out with 1 mmol of alkyne, 0.03 equiv of $RuO_2$, and a 3:1 ratio of $NaHCO_3$ and Oxone, in 15 mL of acetonitrile, 10 mL of water, and 3 mL of ethyl acetate at room temperature for 1 h. [b] Yield of isolated product. [c] Acetone instead of acetonitrile. [d] THF instead of acetonitrile. [e] Yield determined by NMR spectroscopy. [f] $RuCl_3$ instead of $RuO_2$. [g] 0.04 equiv of $RuO_2$. [h] Yield determined by GC.

---

[†] The University of Hong Kong.

[‡] Fudan University.

(1) (a) Long, L. *Chem. Rev.* **1940**, 27, 437. (b) Bailey, P. S.; Chang, V. S.; Kwie W. W. L. *J. Org. Chem.* **1962**, *27*, 1198. (c) Yang, N. C. C.; Libman, J. *J. Org. Chem.* **1974**, *39*, 1782. (d) Ando, W.; Miyazaki, H.; Ito, K.; Auchi, D. *Tetrahedron Lett.* **1982**, *23*, 555. (e) Silbert, L. S.; Foglia, T. A. *Anal. Chem.* **1985**, *57*, 1404.

(2) (a) Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1979**, *44*, 2726. (b) Lie Ken Jie, M. S. F.; Kalluri, P. *Lipids* **1996**, *31*, 1299. (c) Lai, S.; Lee, D. G. *Tetrahedron* **2002**, *58*, 9879.

(3) (a) Gopal, H.; Gordon, A. J. *Tetrahedron Lett.* **1971**, *12*, 2941. (b) Mukai, C.; Miyakawa, M.; Hanaoka, M. *Synlett* **1994**, 165. (c) Griffith, W. P.; Shoair, A. G.; Suriaatmaja, M. *Synth. Commun.* **2000**, *30*, 3091. (d) Cornely, J.; Ham, L. M. S.; Meade, D. E.; Dragojlovic, V. *Green Chem.* **2003**, *5*, 34.

(4) Ballistreri, F. P.; Failla, S.; Spina, E.; Tomaselli, G. A. *J. Org. Chem.* **1989**, *54*, 947.

(5) Zhu, Z. L.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7728.

(6) Sawaki, Y.; Inoue, H.; Ogata, Y. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1133.

(7) Moriarty, R. M.; Penmasta, R.; Awasthi, A. K.; Prakash, I. *J. Org. Chem.* **1988**, *53*, 6124.

10.1021/jo0357925 CCC: $27.50 © 2004 American Chemical Society
Published on Web 02/26/2004

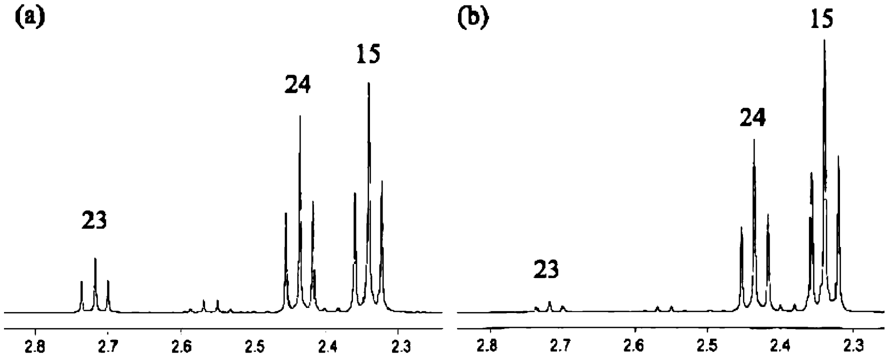


**FIGURE 1.** $^1$H NMR spectra of the crude products obtained after the ruthenium-catalyzed oxidation of **3** with (a) 1 equiv of Oxone and (b) 1.8 equiv of Oxone.

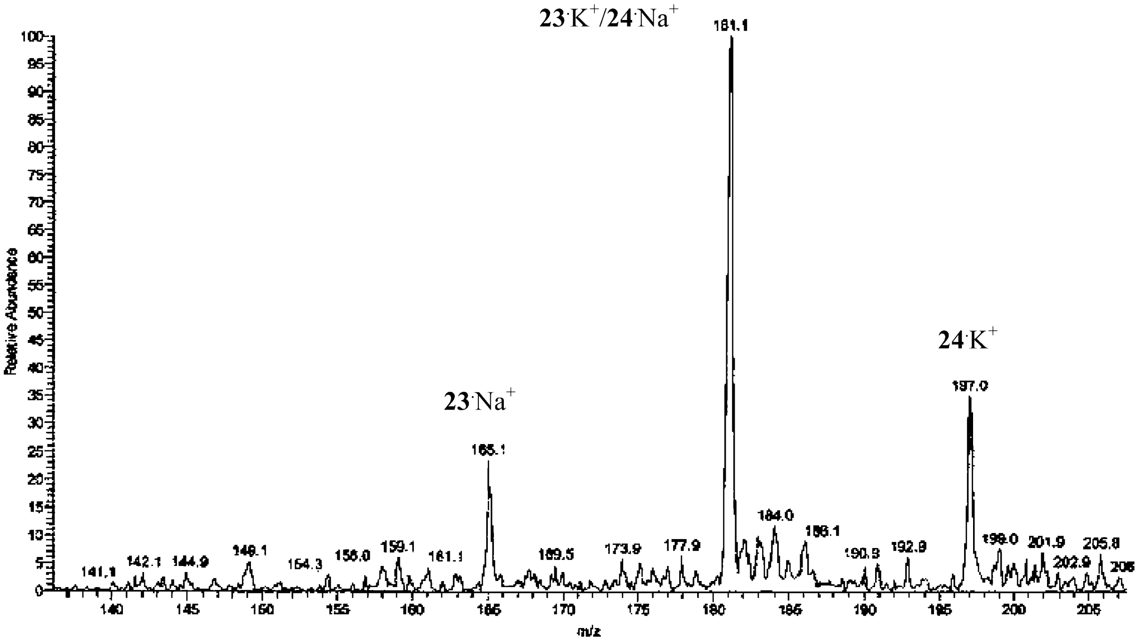


**FIGURE 2.** ESI-MS spectrum of the crude product obtained after oxidation of **3** with 1.8 equiv of Oxone.

It is known that peroxomonosulfuric acid oxidizes $\alpha$-diketones to carboxylic acids[8] and that $\alpha$-diketones are generated from the oxidation of alkynes by using a catalytic amount of $RuO_2$ together with a co-oxidant.[3a] We envisioned that a combination of $RuO_2$ and Oxone ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) could be used to oxidize alkynes to carboxylic acids under mild and neutral conditions. Previously, we reported that alkenes can be oxidized to aldehydes by Oxone in a reaction catalyzed by $RuCl_3$ in a $NaHCO_3$-buffered $CH_3CN/H_2O$ solvent system.[9] Here, we report that a modified reaction system can be applied to oxidize both terminal and internal alkynes to carboxylic acids in excellent yield (Scheme 1).

The new protocol, exemplified in Scheme 1, involves the use of acetonitrile, water, and ethyl acetate (volume ratio 15:10:3) as the solvent system, ruthenium dioxide as the catalyst, Oxone as the terminal oxidant, and sodium bicarbonate as the buffer that maintains the neutral conditions. Ethyl acetate was present to improve the solubility of the substrates, and from solvent screening, we found that acetonitrile was superior as the cosolvent to either acetone or THF (Table 1, entries 1−3). Another ruthenium source, $RuCl_3$, also performed well as a catalyst in the oxidative cleavage of **1** (99% yield of **2**, Table 1, entry 4).

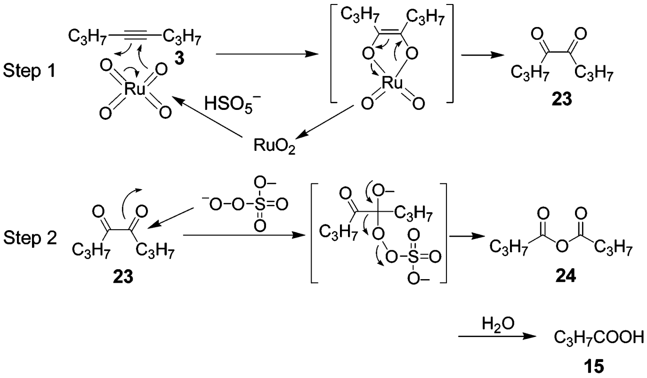
Next we investigated the oxidative cleavage of alkynes possessing different substituents: alkyl (**3**−**5**), aromatic ring (**6**−**8**), ester (**9**), ether (**10** and **11**), silyl ether (**12**), ketone (**13**), and chloride (**14**) units (entries 5−16). In most cases, we achieved clean reactions (except for **8** and **11**) and excellent yields, and no column purifications were needed after workup since almost no side products could be detected in the NMR spectra of the crude products. The aromatic rings of **6**−**8**, the ester group of **9**, the simple ether group of **10**, and the TBDPS group of **12** were all stable in this system. The benzyl ether (**11**) was further oxidized at the benzylic position to afford the benzoic ester as a side product in 14% yield. We attribute the relatively low yield of entry 10 to the stability of benzil, which was detected in the crude NMR spectrum and could be removed by a modified workup.[10] The

---

(8) Panda, R.; Panigrahi, A. K.; Patnaik, C.; Sahu, S. K.; Mahapatra, S. K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1363.

(9) Yang, D.; Zhang, C. *J. Org. Chem.* **2001**, *66*, 4814.

**SCHEME 2. Proposed Mechanism for the Oxidation of Alkynes to Carboxylic Acids**



formation of the lactone in entry 16 resulted from an intramolecular $S_N2$ substitution reaction of the chloride by the carboxylate anion generated at neutral pH. The good solubility of **15** and **22** in water resulted in some loss of these products during aqueous workup (entries 5 and 16). Even though the electron-withdrawing carbonyl group deactivates the carbon−carbon triple bond of **13**, its alkyne cleavage proceeded smoothly upon the addition of 6 equiv of Oxone (entry 15).

To highlight the utility of this reaction, the oxidative cleavage of **1** was carried out successfully on a 20 mmol (4 g) scale. Although 10% heptanoic acid anhydride remained after 2 h, further hydrolysis for 1 h under acidic conditions afforded product **2** cleanly (99% yield). We also found that 6.5 equiv of $NaIO_4$, rather than Oxone/$NaHCO_3$, could be used as a co-oxidant in our reaction system to cleave some alkynes, such as **3** and **9**, to their corresponding carboxylic acids in good yields (>80%) within 3 h. For the oxidation of **1**, however, more than 40% of tetradecane-7,8-dione was present after 4 h because of its slow cleavage by $NaIO_4$.

The oxidative cleavage of alkynes to carboxylic acids using the Oxone/$RuO_2$ system is likely to proceed in two steps (Scheme 2). First, alkyne **3** is oxidized to the α-diketone **23** by the $RuO_4$ generated in situ by the reaction of $RuO_2$ with Oxone, and then **23** undergoes a Baeyer−Villiger-type oxidation by peroxymonosulfate to form acid anhydride **24**, which, upon aqueous hydrolysis, generates the product, acid **15**.

We carried out $^1H$ NMR spectroscopy and ESI-MS experiments to identify the reaction intermediates. When an insufficient amount (e.g., 1−1.8 equiv) of Oxone was used,[11] 4,5-octanedione (**23**) and butyric acid anhydride (**24**) were observed in the $^1H$ NMR spectrum after 4-octyne **3** was oxidized for 20 min (Figure 1). The signals of **23** decreased significantly when the amount of Oxone was increased from 1 to 1.8 equiv, and it disappeared in the end when 3.3 equiv of Oxone was used (Table 1, entry 5). After the oxidation of **3** by 1.8 equiv of Oxone for 20 min, the reaction mixture was diluted with methanol/water and subjected to ESI-MS analysis. We detected three peaks at *m*/*z* 165.1, 181.1, and 197.0, which correspond to the ions **23**·$Na^+$, **23**·$K^+$/**24**·$Na^+$, and **24**·$K^+$, respectively (Figure 2).

In conclusion, we have developed an efficient $RuO_2$−Oxone−$NaHCO_3$ oxidation system, in $CH_3CN/H_2O$/EtOAc, that can transform both terminal and internal alkynes to the corresponding carboxylic acids in excellent yields. Further research to apply this reaction to the construction of chiral carboxylic acids and their derivatives is in progress.

## Experimental Section

**General Procedure for the Oxidation of Alkynes to Carboxylic Acids by $RuO_2$/Oxone.** Sodium bicarbonate (9.9 mmol) and Oxone (3.3 mmol) were added to a stirred solution of alkyne (1 mmol) in $CH_3CN/H_2O$/EtOAc (15:10:3 mL). Ruthenium dioxide (0.03 mmol) was added 3 min later. After being stirred for 1 h, the reaction was quenched with 10% sodium bisulfite solution, acidified with 2 N HCl solution to pH < 2, and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated in vacuo to give the crude products.

**Acknowledgment.** This work was supported by The University of Hong Kong, the Hong Kong Research Grants Council, and the National Natural Science Foundation of China (Project No. 20202001). We thank Yu-Hui Zhang for help in ESI-MS analysis. D.Y. acknowledges the Bristol-Myers Squibb Foundation for an Unrestricted Grant in Synthetic Organic Chemistry and the Croucher Foundation for a Croucher Senior Research Fellowship Award.

**Supporting Information Available:** Synthetic schemes and characterization data of compounds **10** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0357925

---

[10] The reaction was quenched with 10% $NaHSO_3$ solution. The mixture was washed four times with saturated $NaHCO_3$. The combined aqueous layers was acidified using 5 N HCl solution to pH < 2, saturated with NaCl, and then extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried over $Na_2SO_4$, and concentrated in vacuo to give the product.

[11] Unless otherwise indicated, a 3:1 ratio of $NaHCO_3$ and Oxone was employed for the oxidative cleavage reactions.