Pergamon

Tetrahedron Letters, Vol. 36, No. 42, pp. 7693-7696, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01638-4

An Efficient and Versatile Method for the Preparation of α-Keto Acid Derivatives from Terminal Alkenes

Yung-Son Hon*† and Wei-Chih Lin

Institute of Chemistry, Academia Sinica, Nankang, Taipei, Taiwan 11529, R. O. C.

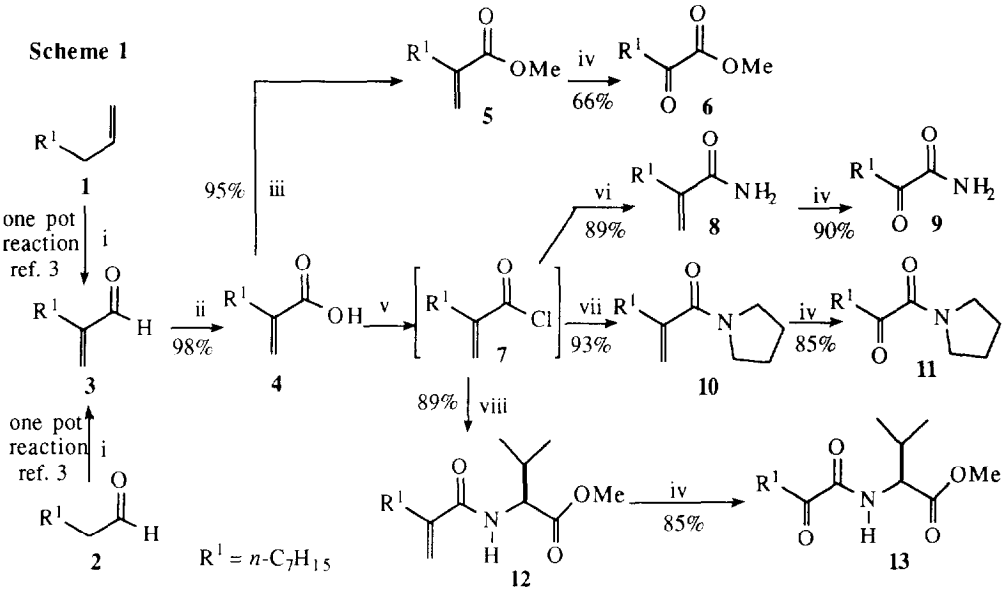
Abstract: Ozonolysis of terminal alkenes followed by reacting with a preheated mixture of CH_2Br_2–Et_2NH affords α-substituted acroleins, which can be converted to α-keto acid derivatives in three steps, under very mild reaction conditions.

α-Keto acid derivatives play important roles not only in organic synthesis but also in biologically active natural products.[1] Oxidation of α-hydroxy esters, oxidative cleavage of the double bond of α,β-unsaturated carbonyl compounds and α-oxidation of carbonyl groups are typical methods for the preparation of α-keto acid derivatives.[2] Likewise, α-keto amides are mostly obtained from amidation of α-hydroxy esters or acids, followed by oxidation. Of the above methods, most lack generality or suffer from lengthy procedures. The use of toxic KCN and drastic hydrolytic conditions limits the application of some methods for the preparation of α-keto acid derivatives with labile functional groups. Recently, we have reported that treatment of ozonides derived from terminal alkenes with a preheated mixture of dibromomethane and diethylamine in dichloromethane affords α-substituted acroleins in good yields.[3] Since the α-methylene group is a masked form of carbonyl group, we envisaged a versatile strategy for the formation of α-keto acid derivatives based on the further functional group transformations of these α-substituted acroleins. In this report, we summarize the results of our work in this direction.

The ozonolysis of 1-decene (**1**) followed by addition of a preheated mixture of CH_2Br_2 and Et_2NH afforded acrolein **3** in 62% yield. Although the high yielding oxidation of acroleins to methyl acrylates by MnO_2 in the presence of KCN in methanol has been reported[4], another approach was investigated in order to avoid using toxic KCN. The oxidation of α-substituted acrolein **3** by Jones reagent gave an inseparable mixture of the acrylic acid **4** in addition to an over-oxidized product. However, a modified procedure using sodium chlorite in the presence of a chlorine scavenger[5] resulted in the acrylic acid **4** formation in 98% yield.[6] The acrylic acid **4** was treated with one equivalent of diazomethane to give the methyl acrylate **5** in excellent yield. The presence of excess diazomethane might result in the further 1,3-dipolar cycloaddition to give Δ^1-pyrazoline.[7] The ozonolysis of methyl acrylate **5** followed by reduction with Ph_3P afforded α-keto ester **6** in 66% yield. Acrylic acid **4** was converted into the acryloyl chloride **7** by thionyl chloride in

excellent yield. There was no double bond isomerization problem even under these acidic conditions. The crude product reacted with ammonium hydroxide to give an excellent yield of acrylamide **8** which was subjected to sequential ozonolysis and reduction to yield the corresponding α-keto amide **9** in 90% yield. The acryloyl chloride **7** also reacts with pyrrolidine or L-valine methyl ester to afford the corresponding acryloyl amides **10** and **12** in excellent yields. In general, the yield for the formation of α-keto amides is better than that of α-keto esters.(Scheme 1)

Scheme 1

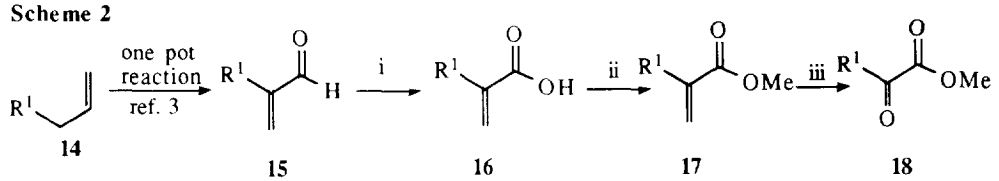


Reagents and Conditions: (i) O_3, CH_2Cl_2, -78 °C; Preheated mixture of Et_2NH and CH_2Br_2 (ii) 2.3 mol equiv $NaClO_2$, *t*-BuOH, 2 mol equiv $NaH_2PO_4 \cdot 2H_2O$, 3 mol equiv $CH_3CH=C(CH_3)_2$ (iii) 1 mol equiv CH_2N_2 (iv) O_3, CH_2Cl_2, -78 °C; then 1 mol equiv Ph_3P (v) 5 mol equiv $SOCl_2$ (vi) NH_3(aq) (vii) pyrrolidine (viii) 1.1 mol equiv L-valine methyl ester, 2 mol equiv Et_3N.

Since the reaction conditions involved in Scheme 1 were very mild, it seemed likely that the sequence might tolerate the presence of the labile groups. Both the keto-olefins **14a** and **14b**[8] can be converted to the α-substituted acroleins **15a** and **15b**, respectively, in good yields where the keto groups are intact (Scheme 2; entries 1 and 2, Table 1). Moreover, the acrolein **15b**, where the quarternary center is adjacent to the α-carbon of the acrolein group, was formed in 61% yield (entry 2). These acroleins can also be converted to α-keto esters in good yields (entries 1 and 2). Hydroxy-olefin **14c** (entry 3), acetoxy-olefin **14d** (entry 4) and iodo-olefin **14e** (entry 5) were also transformed into the corresponding α-keto ester derivatives in good yields *via* similar way. The only exception was that the reducing agent in the ozonolysis of acrylate **17c** was methyl sulfide rather than triphenylphosphine. This was because the polarity of α-keto ester **18c** was close to triphenylphosphine oxide on thin layer chromatography. In order to obtain a good separation by column chromatography, α-keto ester **18c** was exposed to the silica gel for a long period of time while eluting with the lower polarity solvent system. This will result in the self

condensation of α-keto ester **18c** catalyzed by silica gel. This obstacle could be overcome by using methyl sulfide as reducing agent, where the DMSO byproduct is easily removed by extraction.

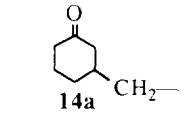
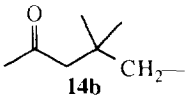
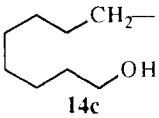
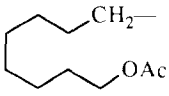
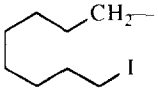
Scheme 2



14 **15** **16** **17** **18**

Reagents and Conditions: (i) 2.3 mol equiv $NaClO_2$, *t*-BuOH, 2 mol equiv $NaH_2PO_4 \cdot 2H_2O$, 3 mol equiv $CH_3CH=C(CH_3)_2$ (ii) 1 mol equiv CH_2N_2 (iii) O_3, CH_2Cl_2, -78 °C; then 1 mol equiv Ph_3P

Table 1: Transformation of terminal alkenes (**14**) to α-keto esters (**18**)

entry	alkene **14** R =	acrolein **15** yield (%)[a]	acrylic acid **16** yield (%)[a]	acrylate **17** yield (%)[a]	α-keto ester **18** yield (%)[a]
1	 **14a**	63	83	96	64
2	 **14b**	61	72	86	71
3	 **14c**	64	85	91	62[b]
4	 **14d**	63	98	87	69
5	 **14e**	68	98	87	67

a. Yields of the isolated product. All compounds were characterized by exact mass spectrometry, IR, and NMR (^1H and ^{13}C). b. Me_2S was used as reducing agent instead of Ph_3P.

In summary, α-keto esters and amides can be prepared in four steps from terminal olefins. The reaction conditions in each step are substantially mild that substrates with labile functional groups can be used. The relatively mild and nontoxic nature of our reaction condition compared with traditional methods indicates that our method might find wide application.

ACKNOWLEDGMENT: We are grateful to the National Science Council and Academia Sinica, Republic of China for financial support.

REFERENCES AND NOTES:

† Permanent address: Department of Chemistry, National Chung Cheng University, Chia-Yi, Taiwan 621, R. O. C. Fax: 886-5-2721040.

1. See the cited references 1–13 in Burkhardt, J. P.; Peet, N. P.; Bey, P. *Tetrahedron Lett.* **1988**, *29*, 3433.
2. For oxidation of α-hydroxy esters or their equivalents, see: (a) Burkhardt, J. P.; Peet, N. P.; Bey, P. *Tetrahedron Lett.* **1990**, *31*, 1385. (b) Peet, N. P.; Burkhart, J. P.; Angelastro, M. R. ; Giroux, E. L.; Mehdi, S.; Bey, P.; Kolb, M.; Neises, B.; Schirlin, D. *J. Med. Chem.* **1990**, *33*, 394. (c) Wipf, P.; Kim, H. Y. *Tetrahedron Lett.* **1992**, *33*, 4275. For oxidative cleavage of the double bond of α,β-unsaturated carbonyl compounds, see: (d) Angelastro, M. R.; Peet, N. P.; Bey, P. *J. Org. Chem.* **1989**, *54*, 3913. (e) Wasserman, H. H.; Ho, W. B. *J. Org. Chem.* **1994**, *59*, 4366. For α-oxidation of carbonyl groups, see: (f) Sliwa, H. *J. Org. Chem.* **1976**, *41*, 160. For metal-catalyzed double carbonylation, see: (g) Sakakura, T.; Yamashita, H.; Kobayashi, T.; Hayashi, T.; Tanaka, M. *J. Org. Chem.* **1987**, *52*, 5733. Miscellaneous, see: (h) Melillo, D. G.; Larsen, R. D.; Mathre, D. J. ; Shukis, W. F.; Wood, A. W.; Colleluori, J. R. *J. Org. Chem.* **1987**, *52*, 5143. (i) Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1981**, *46*, 211. (j) Creary, X. *J. Org. Chem.* **1987**, *52*, 5026. (k) Takahashi, T.; Okano, T.; Harada, T.; Imamura, K.; Yamada, H. *Synlett* **1994**, 121. See also: (i) Barton, D.; Ollis, W. D. *Comprehensive Organic Chemistry*, Pergamon Press, Oxford,1979, Vol. 2, p 779-781.
3. Hon, Y. S.; Chang, F. J.; Lu, L. *J. Chem. Soc., Chem. Commun.* **1994**, 2041.
4. Corey, E. J.; Gilman, N. W.; Ganem, B. E. *J. Am. Chem. Soc.* **1968**, *90*, 5616.
5. Bal, B. S.; Childers, W. E.,Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
6. A typical procedure is as follows. To a solution of aldehyde **2** (2.57g, 16.64 mmol) in 60 mL of *t*-butyl alcohol and 5.3 mL of 2-methyl-2-butene (3.50 g, 49.93 mmol) was added a solution of sodium chlorite (3.46 g, 38.28 mmol) and sodium dihydrogenphosphate (5.19 g, 33.29 mmol) in 22 mL of water dropwise over a 10 min period. The pale yellow reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was concentrated, the residue then dissolved in 30 mL of water and this extracted with 100 mL of hexane. The aqueous layer was acidified to pH 3 with 2N HCl and extracted with two 50 mL portions of ether. The combined ether layers were washed with 50 mL of water, dried with Na_2SO_4 and concentrated to give 2.70 g of spectroscopically pure product **3**.
7. "1,3-Dipolar Cycloaddition Chemistry" edited by Padwa, A., John Wiley & Sons, New York, 1984, Vol. 1, Chapter 4.
8. Sakurai, H.; Hosomi, A.; Hayashi, J. *Org. Synth.* , **1990**, *Coll. Vol. 7*, 443.

(*Received in China* 4 *June* 1995; *accepted* 5 *August* 1995)