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An efficient method for synthesis of α-keto acid esters from terminal alkynes

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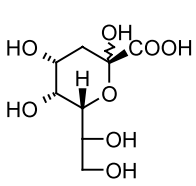
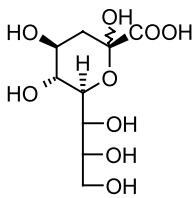
Abstract—α-Keto acid esters can be easily prepared in high yields in two steps from terminal alkynes via bromination and oxidation. This strategy provides a versatile access to the synthesis of biologically important natural products with an α-keto acid moiety.

α-Keto acid esters are found in some important natural products, such as the 3-deoxy-2-ulosonic acids and their derivatives KDO (**1**), KDN (**2**) and sialic acid (**3**), and also in some key intermediates for the synthesis of bio-active compounds. During the chemical synthesis of these compounds several methodologies for building up this moiety have been developed, including ozonolysis of α-methylene esters[1] or oxidation of α-alkoxy esters with MoO_5·Py·HMPA (MoOPH) in the presence of strong base.[2] However, a more convenient and more straightforward synthetic method for the synthesis of α-keto esters is still in need. Terminal alkynes are common and can be easily introduced into synthetic intermediates. In 1995, we developed a diastereoselective propargylation,[3] where a terminal alkyne was easily introduced into protected polyhydroxylated molecules. Considering this background we have developed a new method for converting terminal alkynes into the corresponding α-keto acid esters.

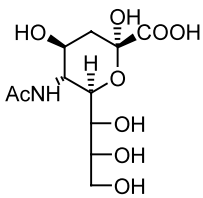
Oxidation of carbon–carbon triple bonds has been demonstrated to be one of the most efficient methods for the preparation of 1,2-dicarbonyl compounds.[4] However, oxidation of terminal alkynes usually gives carboxylic acids with concurrent loss of one carbon atom.[5] The ^{t}BuOOH/OsO_4 oxidant system is known to be able to oxidize trimethylsilylacetylenes[6] or 3-halopropynes[7] to produce α-keto acid esters but only in moderate yields (40–60%) and requires long reaction times (2–4 days). The use of toxic OsO_4 also limits the application of such methods in the preparation of α-keto acid esters. Moreover, Zamojski[8] found that oxidation of substrates substituted by carbohydrate derivatives did not give any expected α-keto acids using the above-mentioned ozonolysis or other systems. It is therefore of interest to investigate new synthetic methods for the preparation of α-keto acid esters from terminal alkynes. Among the variety of oxidation methods, permanganate oxidation[9] was the most attractive, due to the availability of the oxidant, mild conditions, and ease of workup. Tatlock has found that potassium permanganate oxidizes alkynyl ethers to α-keto esters,[10] while substituted alkynyl ethers[11,12] are difficult to prepare from terminal alkynes such as the homopropargylic sugar alcohols obtained by propargylation. Considering the versatility of terminal alkynes in organic synthesis, we were attracted to the use



KDO, **1**



KDN, **2**



N-acetylneuraminic acid, **3**
(Sialic acid)

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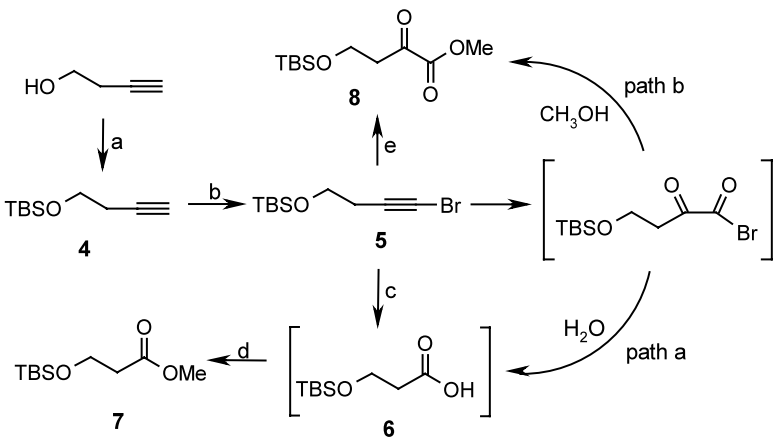
of $KMnO_4$ as oxidant and anticipated that oxidation of bromoalkynes would provide α-keto acid esters. In this letter, we are pleased to report our findings employing this strategy.

Our initial efforts focused on examining the oxidation of bromoalkynes with $KMnO_4$ (Scheme 1). Starting from 3-butyn-1-ol, protection of the hydroxyl group as its *tert*-butyldimethylsilyl ether proceeded in 96% yield. The terminal alkyne **4** was then converted to the corresponding bromoalkyne **5** by reaction with 40 mol% silver nitrate and *N*-bromosuccinimide (2 equivalents) in acetone in high yield (84%). Initially the oxidation of **5** was performed in aqueous acetone with $KMnO_4$ (3 equiv.), $NaHCO_3$ (0.6 equiv.) and $MgSO_4$ (2 equiv.) at 0°C according to the literature procedure.[9,10] After TLC showed the disappearance of the starting material, the resulting carboxylic acid was converted to the methyl ester with diazomethane. Unfortunately, we found that the reaction gave the decarbonyl compound **7**[13] in about 33% yield as the only isolable product. According to the mechanism[14] of oxidation of alkynes with $KMnO_4$, this reaction had probably proceeded via an α-keto acyl bromide intermediate, which was hydrolyzed to the unstable α-keto acid to provide the decarbonyl compound **6** in aqueous acetone (Scheme 1, path a). We thought that this unwanted process would be suppressed if the reaction was performed in aqueous methanol (Scheme 1, path b). The oxidation was then run in methanol/water (1:1) under similar conditions. We found that the reaction was complete in 30 min at 0°C and afforded smoothly the α-keto methyl ester **8**[15] in 90% yield.

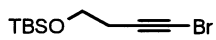
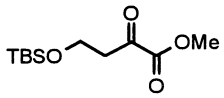
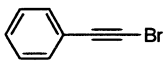
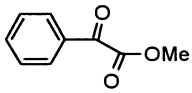
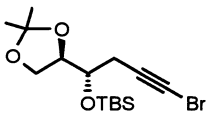
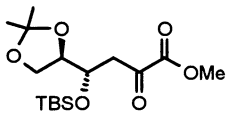
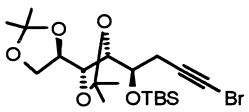
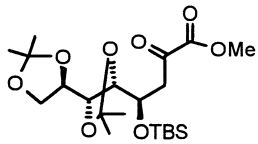
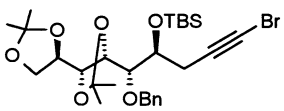
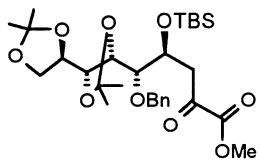
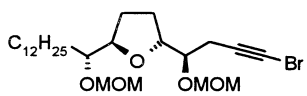
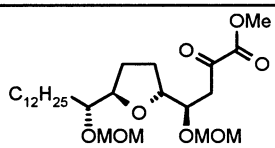
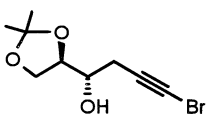
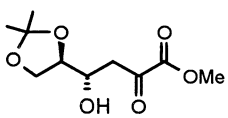
The success of the permanganate oxidation of bromoalkyne **5** prompted us to examine further the scope and the compatibility of the reaction with carbohydrate derived terminal alkynes. A summary of the results of our investigation is given in Table 1. The majority of the substrates (entries 3, 4 and 5) utilized were obtained by propargylation of the corresponding sugar derived aldehyde followed by protection of the hydroxyl group (except for entry 7), while the substrate used for entry 6 was a segment in the synthesis of annonacin previously reported by this group.[16] In most cases (entries 1–5), both bromination and oxidation of the terminal alkynes proceeded smoothly in good to excellent yields. Protecting groups that were sensitive to acid or base were not affected under these conditions. The oxidation of an alkyne containing substituents with a long fatty chain (entry 6) gave a slightly lower yield (68%) in the oxidation reaction and some starting material was recovered due to the poor solubility. We also explored the oxidation in the presence of an unprotected secondary hydroxyl group (entry 7), but only complex and inseparable adducts were obtained. Attempts to oxidize the bromoalkyne in pure methanol failed, and no desired product was detected. TLC showed that deprotection of the adducts occurred owing to the stoichiometric amount of HBr produced in the reaction which could not be removed efficiently.

In summary, this two-step (bromination and permanganate oxidation) reaction sequence presents an efficient method to convert terminal alkynes to α-keto acid esters. The mild reaction conditions offers the potential for the use of this method in the synthesis of complex molecules. It is anticipated that this methodology will have versatile applications in the practical syntheses of biologically important natural products and their intermediates containing α-keto acid segments. Studies on the application of this methodology for the synthesis of 3-deoxy-2-ulosonic acids are underway in this laboratory and will be reported in due time.



Scheme 1. *Reagents and conditions*: (a) TBSCl, DMF, imidazole, rt, 96%; (b) NBS (1.5 equiv.), $AgNO_3$ (0.4 equiv.), acetone, 84%; (c) $KMnO_4$ (3 equiv.), $NaHCO_3$ (0.6 equiv.), $MgSO_4$ (2 equiv.), acetone–H_2O (1:1); (d) CH_2N_2, ether, 0°C, 33% (two steps); (e) $KMnO_4$ (2 equiv.), $NaHCO_3$ (0.5 equiv.), $MgSO_4$ (2 equiv.), MeOH–H_2O (1:1), 90%.

Table 1. Bromination[a] and oxidation[b] of terminal alkynes to α-keto acid esters

Entry	Bromoalkynes	Yield[c] (%)	α-Keto acid esters	Yield[c] (%)
1		84		90
2		83		93
3		85		90
4		86		87
5		82		85
6		94		68
7		81		No[d]

[a] The bromination of the terminal alkynes was realized by reaction with silver nitrate (0.3–0.4 equivalents) and *N*-bromosuccinimide (1.5–2.0 equivalents) at room temperature for 10–20 h.

[b] The oxidation of the bromoalkynes was run in methanol and water (1:1) at 0°C to room temperature for 30 min to 2 h with potassium permanganate as oxidant, and the solution was buffered by addition of $NaHCO_3$ (about 0.6–1.0 equiv.) and $MgSO_4$ (2 equiv.).

[c] Yields refer to isolated products after chromatography on silica gel.

[d] The oxidation reaction gave complex adducts which could not be separated by chromatography.

Acknowledgements

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References

1. For example: (a) Gordon, D. M.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 7937; (b) Chan, T.-H.; Lee, M.-C. *J. Org. Chem.* **1995**, *60*, 4228; (c) Jiang, S.; Rycroft, A. D.; Singh, G.; Wang, X.-Z.; Wu, Y.-L. *Tetrahedron Lett.* **1998**, *39*, 3809.
2. For example: (a) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71; (b) Li, L.-S.; Wu, Y.-L.; Wu, Y.-K. *Org. Lett.* **2000**, *2*, 891.

3. Wu, W.-L.; Yao, Z.-J.; Li, Y.-L.; Li, J.-C.; Xia, Y.; Wu, Y.-L. *J. Org. Chem.* **1995**, *60*, 3257.
4. (a) For a general review, see: Haines, A. H. In *Methods for the Oxidation of Organic Compounds*; Academic Press: London, 1985, p. 153; (b) Che, C.-M.; Yu, W.-Y.; Chan, P.-M.; Cheng, W.-C.; Peng, S.-M.; Lau, K.-C.; Li, W.-K. *J. Am. Chem. Soc.* **2000**, *122*, 11380–11392; (c) Dayan, S.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2000**, *65*, 8816–8818; (d) Walsh, C. J.; Mandal, B. K. *J. Org. Chem.* **1999**, *64*, 6102–6105; (e) Präler, O. C.; Sauer, J. *Tetrahedron Lett.* **1998**, *39*, 8821; (f) Zibuck, R.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 237–240; (g) Torii, S.; Inokuchi, T.; Hirata, Y. *Synthesis* **1987**, 377–379; (h) Lee, D. G.; Lee, E. J.; Brown, K. C. *ACS Symp. Ser.* **1987**, *326*, 82–95; (i) Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1983**, *105*, 7755.
5. (a) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7728–7732; (b) Eisaku, N.; Hisaji, T.; Yoshio, O. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 309–311; (c) Ishii, Y.; Sakata, Y. *J. Org. Chem.* **1990**, *55*, 5545–5547; (d) Ballistreri, F. P.; Failla, S.; Spina, E.; Tomaselli, G. A. *J. Org. Chem.* **1989**, *54*, 947–949; (e) Ballistreri, F. P.; Failla, S.; Tomaselli, G. A. *Stud. Org. Chem.* (Amsterdam), 1988, *33* (Role Oxygen Chem. Biochem.), 341–346; (f) Moriarty, R. M.; Penmasta, R.; Awasthi, A. K.; Prakash, I. *J. Org. Chem.* **1988**, *53*, 6124–6125; (g) Ballistreri, F. P.; Failla, S.; Tomaselli, G. A. *J. Org. Chem.* **1988**, *53*, 830–831; (h) Mueller, P.; Godoy, J. *Helv. Chim. Acta* **1981**, *64*, 2531–2533.
6. Page, P. C.; Rosenthal, S. *Tetrahedron Lett.* **1986**, *27*, 1947–1950.
7. Chen, C.; Crich, D. *J. Chem. Soc., Chem. Commun.* **1991**, 1289–1290.
8. Pakulski, Z.; Zamojski, A. *Tetrahedron* **1997**, *53*, 2653–2666.
9. (a) Srinivasan, N. S.; Lee, D. G. *J. Org. Chem.* **1979**, *44*, 1574; (b) Lee, D. G.; Chang, V. S. *J. Org. Chem.* **1979**, *44*, 2726–2730.
10. Tatlock, J. H. *J. Org. Chem.* **1995**, *60*, 6221–6223.
11. The alkynyl ethers Tatlock used were synthesized by the reaction of the corresponding electrophiles with lithioethoxyacetylene according to the methods reported by Raucher (Raucher, S.; Bray, B. L. *J. Org. Chem.* **1987**, *52*, 2332–2333).
12. Tanaka, R.; Rodgers, M.; Simonaitis, R.; Miller, S. I. *Tetrahedron* **1971**, *27*, 2651–2669.
13. The NMR data of **7**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.90 (2H, t, $J=6.6$ Hz), 3.69 (3H, s), 2.54 (2H, t, $J=6.6$ Hz), 0.89 (9H, s), 0.06 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 59.1, 51.5, 37.9, 25.8 (3C), 18.2, −5.5 (2C). EIMS (m/z, %): 219 (M^++1, 8.46), 203 (M^+−Me, 38.65), 187 (41.36), 161 (100.00). IR (film): 2951, 1742, 1259, 1170, 1021, 842 cm^{-1}.
14. (a) Simandi, L. I.; Jaky, M. *Tetrahedron Lett.* **1970**, 3489–3492; (b) Lee, D. G.; Lee, E. J.; Chandler, W. D. *J. Org. Chem.* **1985**, *50*, 4306–4309.
15. The NMR data of **8**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.96 (2H, t, $J=6.0$ Hz), 3.86 (3H, s), 3.04 (2H, t, $J=6.0$ Hz), 0.86 (9H, s), 0.05 (6H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 162.3, 58.4, 53.1, 42.5, 25.9 (3C), 18.3, −5.6 (2C). EIMS (m/z, %): 245 (M^+−1, 1.35), 205 (1.98), 159 (38.46), 89 (51.57), 75 (100.00), 43 (10.21). IR (film): 2957, 2859, 1758, 1733, 1465, 1258, 1110, 836, 778 cm^{-1}. Elemental analysis calcd for $C_{11}H_{22}O_4Si$: C, 53.66; H, 8.94. Found: C, 53.97; H, 8.87.
16. Hu, T.-S.; Wu, Y.-L.; Wu, Y. *Org. Lett.* **2000**, *2*, 887–889.