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A Ruthenium-Catalyzed, Novel and Facile Procedure for the Conversion of Vicinal Dihaloalkenes to α-Diketones

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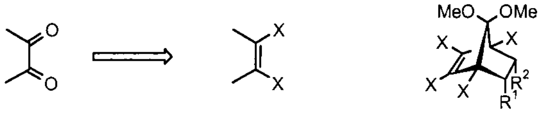
The plenitude of functional groups along with the vast array of methodologies to create, interconvert, and utilize them in a variety of bond forming reactions serve as an important asset for designing chemical synthesis of any target molecule. The α-diketones, a powerful assembly of two adjacent carbonyl groups, are of great interest because of their wide-ranging applications.[1] α-Diketones exhibit interesting photochemistry,[2] are used as flavorants,[3] serve as precursors for ligands in transition metal chemistry,[4] and are used in the preparation of variety of heterocycles[5] and natural products.[6] α-Diketones also function as the key elements in the Weiss reaction[7] and in the construction of rigid molecular assemblies (molecular wires, rods, etc.) based on "block" chemistry.[8] Some of the common methods to obtain α-diketones are the following: (i) oxidation of α-hydroxyketones,[9] (ii) oxidation of alkynes,[10] and (iii) oxidation of α-methylene ketones.[11] Although controlled oxidation of alkenes is difficult, $KMnO_4/Ac_2O$ was reported[12] to give low to moderate yields of α-diketone along with side products. However, the method is not suitable for small cyclic (below cyclooctene) and bicyclic systems.

Scheme 1



X=Cl or Br

1 X=Cl or Br

It transpired to us that vicinal dihaloalkenes could serve as masked α-diketones (Scheme 1).[13] We particularly chose easily accessible[14] substrates **1** because the tetrachloro derivatives of **1** have been serving as exceptionally powerful templates for the synthesis of numerous complex natural as well as aesthetically pleasing unnatural products.[15] A careful literature search revealed that the vicinal dihaloalkene moiety in **1** is quite robust and unreactive toward several reagents,[16] including OsO_4 oxidation conditions.[17] It is interesting to note that the presence of halogens in **1** is rather a compulsion than choice[18] and a complete reductive dehalogenation is almost invariably followed. We recently reported selective utilization of halogens in **1** for C−C bond formation at the bridgehead.[18] In continuation of our efforts to use halogens in **1** as useful functional groups, we developed a novel, facile, and extremely efficient methodology employing catalytic $RuCl_3 \cdot 3H_2O$ and $NaIO_4$ as stoichiometric cooxidant[19] and report herein our results.

The substrates **1a**−**21a** were subjected to ruthenium tetroxide (generated in situ) oxidation employing $RuCl_3 \cdot 3H_2O/NaIO_4$ in acetonitrile−water (6:1). The results are summarized in Table 1. In all the cases the reaction proceeds smoothly and efficiently, providing good to excellent yield of crystalline, yellow α-diketones (entries 1−6, 13−18) or the products derived from them (entries 7−12, 19−21).[20] Reaction times varied considerably, but in general tetrabromo derivatives required relatively longer time compared with tetrachloro derivatives and so is the case with disubstituted versus monosubstituted (R^2 = H) derivatives in each series. It is interesting to note that only one of the two primary hydroxyl groups in **7a** and **19a** was partially affected, forming aldehyde first, followed by lactol formation and further oxidation to furnish lactones **7c** and **19c**. While the lactol thus formed is responsible for hemiacetals **7d** and **19d**. The symmetric bis lactones **7e** and **19e** originate from the glycol cleavage of the intermediates **7f** and **19f**. On the other hand, mono-hydroxymethyl-substituted derivatives **8a** and **20a** exclusively furnished the corresponding hemiacetals in high yields. The acid **9a** also gave a similar result. Protection of hydroxyl groups in all these cases furnished the normal α-diketone product (entries 3, 15, and 18). It is remarkable to note that the conversion of sensitive substrates **6a** and **17a** was smoothly accomplished in excellent yield.

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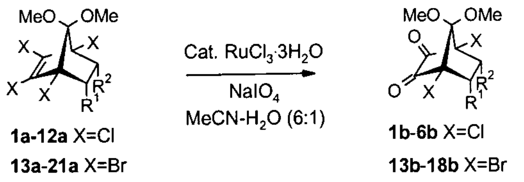
(20) All new compounds were satisfactorily characterized by spectroscopic methods including elemental analysis.

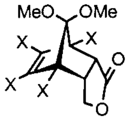
10.1021/ja001956c CCC: $19.00

Table 1. Ruthenium-Catalyzed Oxidation of Vicinal Dihaloalkenes to α-Diketones[a]

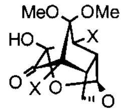


entry	substrate	R^1, R^2	product	time	yield (%)[b]
1	**1a**	CO_2Me	**1b**	13 h[c]	95[d]
2	**2a**	CO_2Me, H	**2b**	10 min	94
3	**3a**	$-CH_2OCH_2OCH_2-$	**3b**	6 h	93
4	**4a**	$-(CH_2)_4-$	**4b**	6 h[c]	83
5	**5a**	Ph, H	**5b**	20 min	96
6	**6a**	OAc, H	**6b**	2 min	98
7	**7a**	CH_2OH	**7c**,**d**,**e**	38 h[c]	21, 30, 34
8	**8a**	CH_2OH, H	**8c**	2 h	76
9	**9a**	CO_2H, H	**9c**	4 h[c]	74
10	**10a**	$-CH_2OC(O)-$	**10c**	5.5 h[c]	78
11	**11a**	$-C(O)-(CH_2)_3-$	**11c**	9 h	90
12	**12a**	$-C(O)-(CH_2)_2-C(O)-$	**12c**	6 h	94
13	**13a**	CO_2Me	**13b**	30 h[c]	93[d]
14	**14a**	CO_2Me, H	**14b**	2 h	89
15	**15a**	$-CH_2OCH_2OCH_2-$	**15b**	6 h	87
16	**16a**	Ph, H	**16b**	10 h	99[d]
17	**17a**	OAc, H	**17b**	20 min	98
18	**18a**	CH_2OAc, H	**18b**	1 h	90
19	**19a**	CH_2OH	**19c**,**d**,**e**	34 h[c]	55, 30, 10
20	**20a**	CH_2OH, H	**20c**	5 h[c]	92
21	**21a**	CHO, H	**21c**	3 h	83[e]

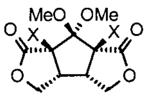
[a] All reactions were run using 7% $RuCl_3 \cdot 3H_2O$ and 150% $NaIO_4$, at 0−5 °C. [b] Isolated yields of analytically pure sample. [c] At 0 °C to room temperature. [d] Based on starting material recovery; 76%, 60%, and 85% conversions, respectively. [e] Mixture of diastereomers (65:35).



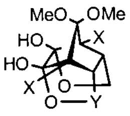
7c X=Cl
19c X=Br



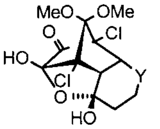
7d X=Cl
19d X=Br



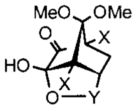
7e X=Cl
19e X=Br



10c X=Cl; Y=C(O)
7f X=Cl; Y=CH_2
19f X=Br; Y=CH_2



11c Y=CH_2
12c Y=C(O)

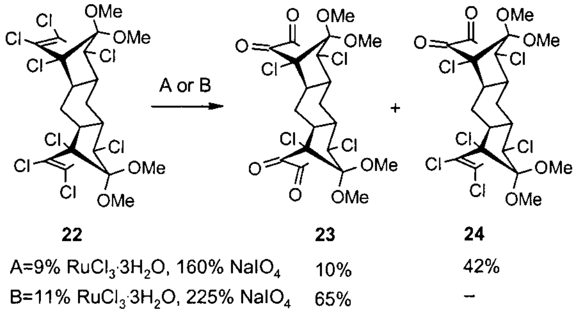


8c X=Cl; Y=CH_2
9c X=Cl; Y=C(O)
20c X=Br; Y=CH_2
21c X=Br; Y=CH(OH)

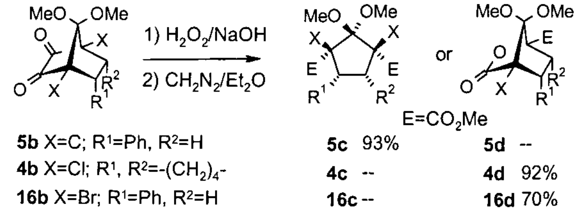
The α-diketone group in these rigid molecules is constrained into a cisoid conformation and therefore one of the carbonyls has a very high tendency to switch to a sp^3-hybridized carbon, preferably through intramolecular hemiacetal formation (vide supra) or hydrate formation. Whenever a suitable substituent, as in **11a**, **12a**, and **21a**, capable of interacting in an intramolecular fashion with the incipient α-diketone monohydrate is present, a stable hydrate in the form of double hemiacetal (**11c**, **12c**, and **21c**) was isolated. In case of **10a**, the initial lactone reorganizes itself into a rigid hemiacetal **10c**.

The versatility of the method was further demonstrated by the facile conversion of bis adduct **22**, obtained from the Diels−Alder reaction between 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene and 1,4-cyclohexadiene,[21] into bis- and mono-α-diketones **23** and **24** (Scheme 2). When 9 mol % ruthenium catalyst and 1.6 equiv of $NaIO_4$ was employed, **23** and **24** were obtained in a ratio of 1:4 in 52% isolated yield. Increasing the catalyst to 11 mol % and co-oxidant to 2.25 equiv furnished exclusively the symmetric, sparingly soluble, yellow bis-α-diketone **23** in 65% yield.

Scheme 2



Scheme 3



The wide-spread occurrence of functionalized cyclopentane derivatives in nature prompted us to seek a direct access to these from the abundantly available **1**, utilizing our methodology. It is known that the oxidation of the double bond in norbornene derivatives (after complete dehalogenation of **1**) affords cyclopentanes devoid of any halogen groups. We considered $KMnO_4$-mediated oxidation[22] on model substrates **5a** and **16a**. Both remained inert even under vigorous conditions (ethyl methyl ketone, reflux). We subsequently examined the H_2O_2/NaOH-mediated cleavage[23] reaction of α-diketones (Scheme 3). In the case of **5b**, an excellent yield of bis(α-chloroester) cyclopentane derivative **5c** was realized. Under identical reaction conditions **4b** and **16b** furnished exclusively bicyclic lactones **4d** and **16d** (single regioisomer), respectively, in high yields through displacement of halogen by carboxylate anion.

In conclusion, we have demonstrated a facile conversion of vicinal dihaloakenes to α-diketones starting from abundantly available, celebrated rigid templates in organic synthesis, **1a**−**21a**. A remarkably expeditious route to symmetric, polycyclic bis(α-diketone) **23** was accomplished. The methodology was elaborated to obtain highly functionalized novel cyclopentane possessing bis(α-chloroester) groups or bicyclic lactones, which are inaccessible via the existing methods.

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Supporting Information Available: Experimental details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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