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Novel PDC catalyzed oxidative rearrangement of tertiary allylic alcohols to β-substituted enones

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ABSTRACT

Novel pyridinium dichromate (PDC) catalyzed oxidative rearrangement for the conversion of tertiary allylic alcohols to ß-substituted enones is described. Using a catalytic amount of PDC with $PhI(OAc)_2$ as a co-oxidant in the presence of magnesium sulfate and water under oxygen was found effective for this rearrangement.

The oxidative rearrangement of tertiary allylic alcohols is a fundamental means for the preparation of β-substituted α,β-unsaturated ketones in natural product synthesis.[1] An oxochromium(VI) based reagent such as pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) is the first choice for the rearrangement.[2] The pathway of the reaction is considered to quite likely be that shown in Scheme 1. First, tertiary allylic alcohol **I** reacts with oxochromium(VI) based reagent to form chromate **II**. The allylic rearrangement of **II** produces the chromate of secondary alcohol **III**, which is then transformed to enone **IV** and oxochromium(IV). Oxochromium(VI) appears to be the most suitable reagent since it acts at both the stage of rearrangement and oxidation. But these reactions require stoichiometric amounts of oxochromium(VI) based oxidants all of which possess considerable toxicity.

Recently, alternative methods have been reported for the reactions shown above. These reactions may be classed as either those caused through use of stoichiometric amounts of oxidant or catalytic amounts of a reagent with co-oxidant. Oxoammonium salts of 2,2,6,6-tetramethylpiperidine 1-oxyl ($TEMPO^+X^-$) oxidation[3] and 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX) oxidation[4] are of the first type reaction while the second type involves combinations of TEMPO and $NaIO_4–SiO_2$,[5] TEMPO, iodosylbenzene (PhIO) and $Bi(OTf)_3$,[6] TEMPO and copper(II) chloride ($CuCl_2$),[6] 2-iodoxybenzenesulfonic acid (IBS) and Oxone® ($2KHSO_5·KHSO_4·K_2SO_4$),[7] and Pt black and H_2O_2.[8] These reagents were used for the oxidation of various tertiary allylic alcohols. However, no suitable reagent for the conversion of cyclohex-2-enols **14a**[9] bearing a bulky substituent at the 6-position to β-substituted enone **14b** has been found in our studies on natural product synthesis.

To develop a more effective reagent than PCC or PDC but with less toxicity, an investigation was made of PDC catalyzed oxidative rearrangement of tertiary allylic alcohols. Studies on several oxochromium(VI) catalyzed oxidations have indicated chromium(VI) oxide (CrO_3) to catalyze the oxidation of primary and secondary allylic alcohols with alkyl hydroperoxide,[10] CrO_3 to catalyze the oxidation of primary and secondary alcohols, benzylic C–H bonds, and arenes with periodic acid (H_5IO_6),[11] and the (salen)chromium complex catalyzed oxidation of primary and secondary allylic (or benzyl) alcohols with PhIO[12] or iodosylbenzene diacetate ($PhI(OAc)_2$).[12] But to date, no application of these reagents to the oxidative rearrangement of tertiary allylic alcohols has been made to our knowledge.

In the present study, the effective transformation of tertiary allylic alcohols to α,β-unsaturated ketones using catalytic amounts of PDC and $PhI(OAc)_2$ as a terminal oxidant was successfully carried out.

The reaction conditions for the PDC catalyzed oxidation of 1-butylcyclohex-2-enol (**1a**) with $PhI(OAc)_2$ to give 3-butylcyclohex-2-enone (**1b**) is shown in Table 1. Reaction of **1a** with 0.01 equiv of PDC and 3.0 equiv of $PhI(OAc)_2$ in CH_2Cl_2 (0.2 M) for 24 h at room temperature under argon atmosphere gave **1b** in 84% yield (entry 1). In this reaction, air or oxygen was found to promote the reactivity of the reagent remarkably, but in all

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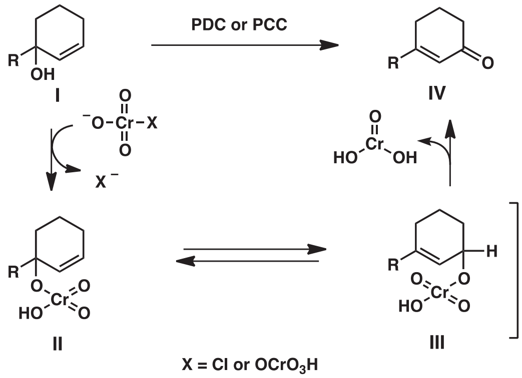
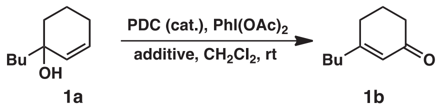


Scheme 1. The reaction pathway of the oxidative rearrangement of tertiary allylic alcohol I to form α,β-unsaturated ketone IV by oxochromium(VI) based reagent.

cases, a small amount of **1a** was recovered (entries 2 and 3). Using 0.05 equiv of PDC and 1.5 equiv of $PhI(OAc)_2$ under oxygen increased the reaction rate and an optimum yield of **1b** was 94% (entry 4). Reproducibility of the reaction, however, was not satisfactory. The addition of 1 equiv of H_2O in this reaction condition was found to improve reproducibility, but the yield of **1b** was slightly less than without H_2O (entry 5). This problem was solved by the addition of 1 equiv of $MgSO_4$, which increases the yield of **1b** to 96% (entry 6). It seems that gradual supply of H_2O is effective for this reaction. However, the exact reason for the effectiveness of a combination of H_2O, $MgSO_4$, and O_2 is not clear. This condition is superior to that commonly used for PDC oxidation in nearly all respects (entry 7). It should be pointed out that the oxidation of **1a** with 1.5 equiv of $PhI(OAc)_2$ without PDC did not occur (entry 8).

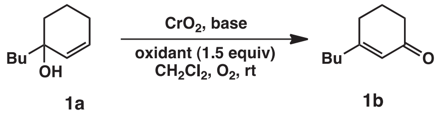
Table 1
Optimization of the reaction conditions for the oxidative rearrangement of allylic alcohol **1a** with pyridinium dichromate in the presence of $PhI(OAc)_2$



Entry	PDC (equiv)	PhI $(OAc)_2$ (equiv)	Additive (equiv)	Condition	Concn (M)	Time (h)	Yield[a] (%)
1	0.01	3.0	–	Ar	0.2	24	84
2	0.01	3.0	–	Air	0.2	1.5	88[b]
3	0.01	3.0	–	O_2	0.2	1	88[b]
4	0.05	1.5	–	O_2	0.5	0.25	94[c]
5	0.05	1.5	H_20 (1.0)	O_2	0.5	0.25	86
6	0.05	1.5	H_20 (1.0) $MgSO_4$ (1.0)	O_2	0.5	0.25	96
7	2.0	–	–	Air	0.2	3	91
8	–	1.5	–	Air	0.2	5	0[d]

[a] Isolated yield.
[b] A small amount of **1a** was recovered.
[c] The best yield, but low reproducibility.
[d] No reaction.

Table 2
Combinations of oxidant and base for chromium(IV) oxide catalyzed oxidative rearrangement of allylic alcohol **1a**



Entry	CrO_2	Base (equiv)	Oxidant	Time (h)	Yield[a] (%)
1	0.1	Pyridine (0.1)	$PhI(OAc)_2$	0.5	94
2	0.1	–	$PhI(OAc)_2$	1	0[b]
3	2.0	–	–	1	0[b]
4	2.0	Pyridine (2.0)	–	1	0[b]
5	0.1	2,6-Lutidine (0.1)	$PhI(OAc)_2$	1	0[b]
6	0.1	DMAP (0.1)	$PhI(OAc)_2$	1	0[b]
7	0.1	$NaHCO_3$ (0.1)	$PhI(OAc)_2$	1	0[b]
8	0.1	MS4A	$PhI(OAc)_2$	1	0[b]
9	0.1	Pyridine (0.1)	PhIO	1	0[b]
10	0.1	Pyridine (0.1)	NaIO	1	0[b]
11	0.1	Pyridine (0.1)	IBX	15	90

[a] Isolated yield.
[b] No reaction occurred.

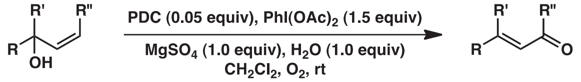
The chromium(IV) generated in the above reactions should be reoxidized to chromium(VI) by $PhI(OAc)_2$. A study was thus made using a combination of chromium(IV) oxide (CrO_2), base, and PhI$(OAc)_2$ instead of PDC in combination with $PhI(OAc)_2$ and the results are shown in Table 2. Using 0.1 equiv of CrO_2, 0.1 equiv of pyridine and 1.5 equiv of $PhI(OAc)_2$ in CH_2Cl_2 (0.5 M) under oxygen atmosphere for the reaction of **1a** provided results essentially the same as for the oxidation described above. Enone **1b** was obtained in 94% yield (entry 1). The oxidation did not proceed without pyridine and/or $PhI(OAc)_2$ (entries 2–4). Pyridine was essential and could not be replaced with 2,6-lutidine, *N*,*N*-dimethylaminopyridine (DMAP), $NaHCO_3$, or MS4A (entries 5–8). Neither PhIO nor $NaIO_4$ was found to function as a co-oxidant (entries 9 and 10). IBX, however, was found to serve as a co-oxidant, but with a lower reaction rate (entry 11). IBX treatment of **1a** in CH_2Cl_2 without the presence of CrO_2 did not cause the oxidative rearrangement.

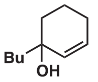
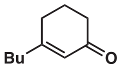
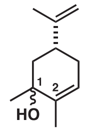
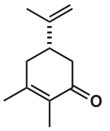
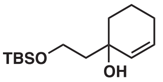
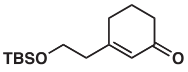
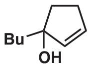
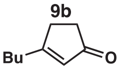
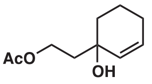
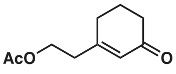
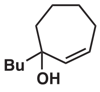
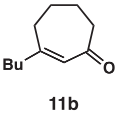
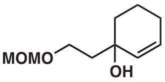
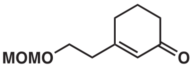
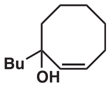
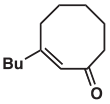
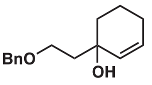
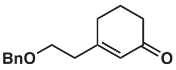
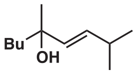
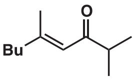
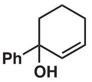
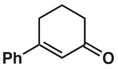
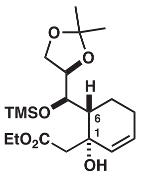
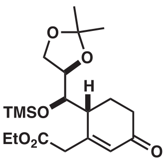
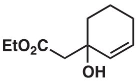
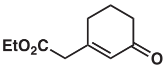
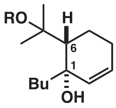
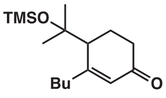
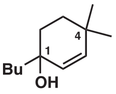
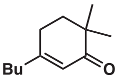
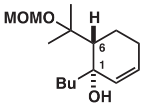
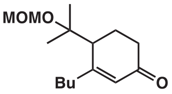
CrO_2 is thus shown to function as a catalyst for the oxidation in the presence of pyridine and $PhI(OAc)_2$ (or IBX) under oxygen.

The PDC catalyzed oxidative rearrangement to various substrates was consequently investigated. Allylic alcohols **2a**–**5a** each bearing a *tert*-butyldimethylsilyloxy, acetyloxy, methoxymethoxy, or benzyloxy group could be converted to the corresponding enones **2b**–**5b** in good yields (Table 3, entries 2–5). In the cases of benzyl alcohol **6a** and ester **7a**, the standard reaction conditions were ineffective for completing the oxidation and the yields of enones **6b** and **7b** were only moderate (entries 6 and 7). 3 equiv of $PhI(OAc)_2$ and the addition of 11 equiv of pyridine in the case of **6a** or 3 equiv of $PhI(OAc)_2$ in the case of **7a**, were found to improve the yields of **6b** and **7b**. Allylic alcohol **8a** bearing a quaternary carbon center at the 4-position smoothly underwent conversion to enone **8b** in high yields (entry 8). The substituent at the 2-position in cyclohex-2-enol **9a** was found to hinder the oxidation and the yield of **9b** was somewhat low (entry 9). Neither transformation of **11a** bearing a cycloheptene ring, **12a** bearing a cyclooctene ring nor acyclic allylic alcohol **13a** to corresponding enones **11b**–**13b** gave satisfactory results, but cyclopent-2-enol **10a** was easily oxidized to **10b** (entries 10–13). PDC and PhI$(OAc)_2$ in combination were effective for bringing about the oxidation of allylic alcohols each possessing a bulky group at the 6-position. The oxidation of **14a**[9] having a number of acid sensitive groups produced enone **14b** in 70% yield (entry 14). The usual PDC oxidation of **14a** gave low yield of **14b** and a small amount of **14a** was recovered. Alcohols **15a** with 2-(trimethylsilyloxy)propan-2-yl group and **16a** with 2-(methoxymethoxy)propan-2-yl group gave 76% yield of **15b** and 92% yield of **16b**, respectively (entries 15 and 16). TEMPO catalyzed oxidation[5] of **15a** with $NaIO_4$–SiO_2 was seen to cause desilylation to give **15c** and the oxidation of **16a** provided **16b** in moderate yields.

The typical experimental procedure for the PDC catalyzed oxidative rearrangement of tertiary allylic alcohol with $PhI(OAc)_2$ is shown in the following. To a solution of alcohol **1a** (77.1 mg, 0.500 mmol) in CH_2Cl_2 (1.0 mL, 0.5 M) was added $MgSO_4$ (60.2 mg,

Table 3
Pyridinium dichromate catalyzed oxidative rearrangement of allylic alcohols with iodosobenzene diacetate



Entry	Substrate	Product	Time (h)	Yield[a] (%)	Entry	Substrate	Product	Time (h)	Yield[a] (%)
1	 **1a**	 **1b**	0.25	96	9	 **9a**[d]	 **9b**	1	49
2	 **2a**	 **2b**	1	87	10	 **10a**	 **10b**	0.5	84
3	 **3a**	 **3b**	1	81	11	 **11a**	 **11b**	1	43
4	 **4a**	 **4b**	1	86	12	 **12a**	 **12b**	1	38
5	 **5a**	 **5b**	1	77	13	 **13a**	 **13b**	1	Trace
6	 **6a**	 **6b**	0.5 1.5	41 84[b]	14	 **14a**	 **14b**	24 12	70[c] 38[e]
7	 **7a**	 **7b**	3 24	51 69[c]	15	 **15a: R = TMS** **15c: R = H**	 **15b**	1 1	76[f] 0[g,h]
8	 **8a**	 **8b**	0.5	90	16	 **16a**	 **16b**	1 1	92 57[g,i]

[a] Isolated yield.
[b] PDC (0.05 equiv), PhI(OAc)$_2$ (3.0 equiv), pyridine (11 equiv), MgSo$_4$ (1.0 equiv), O$_2$ (balloon), CH$_2$Cl$_2$ (0.2 M).
[c] PDC (0.05 equiv), PhI(OAc)$_2$ (3.0 equiv), H$_2$0 (1.0 equiv), O$_2$ (balloon), CH$_2$Cl$_2$ (0.1 M).
[d] A 7:1 diastereomeric mixture.
[e] PDC (3 equiv), MS4A, CH$_2$Cl$_2$ (0.2 M).
[f] 14% of **15a** was recovered.
[g] TEMPO (0.01 equiv), NaIO$_4$–SiO$_2$ (2 equiv), CH$_2$Cl$_2$ (0.1 M).
[h] Diol **15c** was obtained quantitatively.
[i] 35% of **16a** was recovered.

0.500 mmol), H$_2$O (9.0 μL, 9.0 mg, 0.50 mmol), PhI(OAc)$_2$ (242 mg, 0.750 mmol) and PDC (9.4 mg, 25 μmol) with stirring. The resulting dark brown mixture was stirred for 15 min at room temperature under oxygen (balloon). This was followed by the addition of saturated aqueous NaHCO$_3$ and 20% aqueous Na$_2$S$_2$O$_3$. After been stirred for 15 min, the suspension was diluted with Et$_2$O. The organic layer was washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/ether = 3.5:1) to give **1b** (73.0 mg, 0.480 mmol, 96%).

In summary, PDC was found an effective catalyst for the oxidative rearrangement of cyclic tertiary allylic alcohols with PhI(OAc)$_2$, MgSO$_4$, and H$_2$O in CH$_2$Cl$_2$. By this method, various 1-alkylcyclohex-2-enols, cyclohex-2-enol bearing a quaternary carbon center at the 4-position and 1-alkylcyclopent-2-enol could be smoothly converted to the corresponding enones and even cyclohex-2-enol

14a bearing a bulky group at the 4-position, the usual PDC oxidation of which gave only low yield of **14b**, could be oxidized to enone **14b** in good yields. CrO_2 could also be used as a catalyst for the oxidative rearrangement in the presence of pyridine and $PhI(OAc)_2$.

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References and notes

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