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PCC-mediated novel oxidation reactions of homobenzylic and homoallylic alcohols

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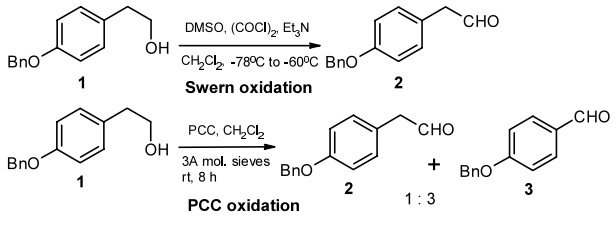
Abstract—A new PCC-mediated carbon–carbon bond cleavage reaction during oxidation of homobenzylic alcohols leading to the formation of benzylic carbonyl compounds has been observed. Homobenzylic alcohols with no benzylic substitution ($R^1 = H$) gave benzylic aldehydes without further oxidation, while those with benzylic substitution ($R^1 = Me$, Et, Ar) gave benzylic ketones. In contrast, homoallylic alcohols gave products arising from double bond migration, *cis*- to *trans*-olefin isomerization and/or allylic oxidation.

Before the studies of Corey and co-workers,[1] the reactivity of PCC had been little investigated. PCC is well known to convert alcohols into aldehydes or ketones with high efficiency.[2a] This reagent also converts tertiary cyclopropyl carbinols into the corresponding β,γ-unsaturated ketones,[2b] 1,4-dienes into dienones,[2c,d] hydroquinone silyl ethers into quinones,[2e] enol ethers to esters and lactones[2f] and oximes to ketones.[2g] Other known important conversions using this reagent are: (i) furan rings undergo oxidative ring expansion,[3a] (ii) Δ^5-3β-tetrahydropyranyl ethers are oxidized to the corresponding carbonyl Δ^4-3,6-diones,[3b] (iii) olefins are oxidized to carbonyl compounds via the oxidation of organoboranes.[3c–g] Furthermore, PCC is well known for selective oxidation of steroidal allylic alcohols,[4a] oxidative cleavage of aryl substituted olefins,[4b] specific oxidative cleavage of allylic and benzylic ethers,[4c] oxidation of benzylic[4d] and active methylene compounds,[4e] oxidative cleavage of 1,4-dioxenyl carbinols to α-hydroxy acids and α-ketoacids,[4f] one-pot oxidation of glycals to lactams,[4g] cleavage of vicinal diols[4h] and modified oxidation of aldehydes to carbamoyl azides/acyl azides or carboxylic acids.[4i] Thus, the varied and numerous oxidative reactions of PCC makes it a versatile oxidant in organic synthesis.[5]

In our recent synthetic endeavor on the total synthesis of the anticoccidial antibiotic (+)-diolmycin A2,[6] we were in need of 2-(4-benzyloxyphenyl)acetaldehyde **2**. Swern oxidation of 2-(4-benzyloxyphenyl)ethanol **1** proceeded smoothly to give 2-(4-benzyloxyphenyl)-acetaldehyde **2** in good yield.

To avoid the work-up procedure involving malodorous dimethylsulfide, we carried out a PCC oxidation. Surprisingly the oxidation of **1** with 1.5 equiv. of PCC afforded a mixture of expected 2-(4-benzyloxyphenyl)-acetaldehyde **2** and 4-benzyloxybenzaldehyde **3** in a 1:3 ratio (Scheme 1).

Thus, the scission of a C–C bond leading to loss of one carbon atom was observed in the PCC oxidation and yet to add to our enthusiasm the end product was still an aldehyde without any further oxidation to the corresponding acid. The product mixture was confirmed by ^1H NMR analysis where the benzylic methylene of **2** was characteristic. The aldehyde proton of **3** appeared as a sharp singlet at δ 10.1 indicating a benzylic aldehyde, while a triplet was seen at δ 9.8 indicating a small amount of homobenzylic aldehyde **2**. Thus, this degradative oxidation involving C–C bond cleavage adds a novel and new oxidation reaction of PCC.



Scheme 1. Swern and PCC oxidations.

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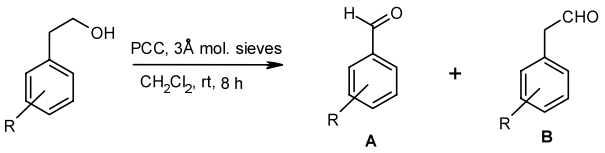
Aimed at achieving a better understanding of this new oxidation reaction, we subjected various homobenzylic alcohols with no benzylic substitution to PCC oxidation. While the initial experiment with 1.5 equiv. of PCC gave a small amount of homobenzylic aldehyde, the major product obtained was benzylic aldehyde (entries 1 and 3, Table 1). Interestingly, when the oxidation was carried out with 3 equiv. of PCC, the benzylic aldehyde was obtained as the sole product. The generality of this reaction was further demonstrated with a variety of aryl substituted homobenzylic alcohols having no benzylic substitution (Table 1).

The product was isolated virtually in pure form without the need for further purification beyond mere filtration and concentration.

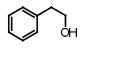
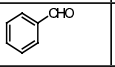
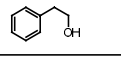
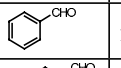
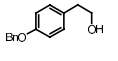
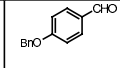
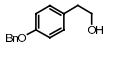
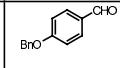
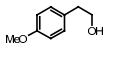
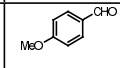
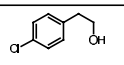
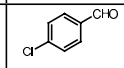
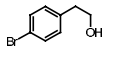
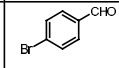
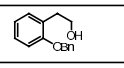
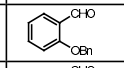
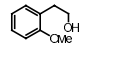
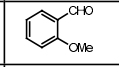
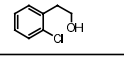
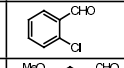
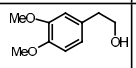
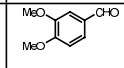
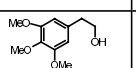
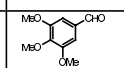
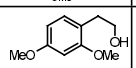
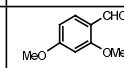
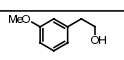
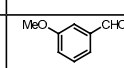
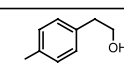
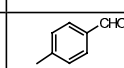
In order to study the scope of this oxidation, we further extended the reaction to homobenzylic alcohols with benzylic substitution (alkyl/aryl) such that the end product would be an aryl ketone. The simplest substrate available was 2-phenyl-1-propanol (obtained via hydroboration of α-methylstyrene) which on oxidative degradation should yield acetophenone as the end product. Thus, the PCC oxidation of 2-phenyl-1-propanol initially with 1.5 equiv. of PCC gave a mixture of acetophenone and 2-phenylpropanal (9:1) respectively (entry 1, Table 2). However, the use of 3 equiv. of PCC, furnished acetophenone as the only product (entry 2, Table 2).

Thus, various homobenzylic alcohols with benzylic substitution (alkyl/aryl) on oxidation with 3–4 equiv. of PCC produced only the aryl ketones in good yields

Table 1. PCC oxidation of homobenzylic alcohols with no benzylic substitution[7]

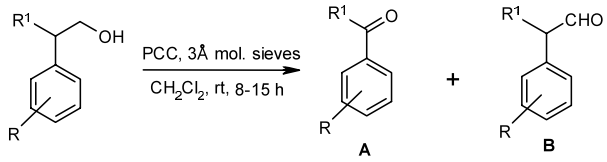


R = H, Cl, Br, OH, OMe, OCH_2Ph, Ar

Entry	Substrate	Eq. of PCC	React. time/h	Major Product	Ratio of **A:B**	Yield %
1		1.5	8		80:20	65[a]
2		3	8		100:0	71
3		1.5	8		75:25	68[a]
4		3	8		100:0	70
5		3	8		100:0	69
6		3	8		100:0	63
7		3	8		100:0	64
8		3	8		100:0	66
9		3	8		100:0	64
10		3	8		100:0	70
11		3	8		100:0	72
12		3	8		100:0	73
13		3	8		100:0	73
14		3	8		100:0	65
15		3	8		100:0	66

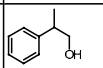
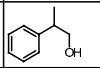
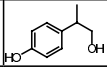
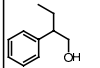
[a]yields refer to the mixture of **A** and **B**

Table 2. PCC oxidation of homobenzylic alcohols with benzylic alkyl/aryl substitution[7]



R = H, Cl, Br, OH, OMe, OCH_2Ph, Ar

R^1 = Me, Et, Ar

Entry	Substrate	Eq. of PCC	React. time/h	Major Product	Ratio of **A:B**	Yield %
1		1.5	8		90:10	70[a]
2		3	8		100:0	71
3		3	12		100:0	63
4		3	10		100:0	68
5		3	8		100:0	63
6		4	12		100:0	75
7		4	12		100:0	63
8		4	15		100:0	66
9		4	15		100:0	67

[a]yields refer to the mixture of **A** and **B**

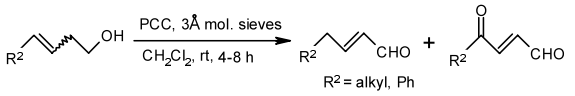
(Table 2). It should be noted that although PCC is commonly employed for the oxidation of benzylic and active methylene compounds, no oxidation of benzylic methylene was observed for the entries 8 and 9 (Table 2), indicating the need for reflux conditions as reported in the literature.[4d]

Encouraged by the finding of C–C bond cleavage during the oxidation reaction mediated by PCC on homobenzylic alcohols, we further proceeded to study the same reaction on homoallylic alcohols. While the PCC-mediated allylic oxidation to α,β-unsaturated carbonyl compounds has been thoroughly investigated, the oxidation of homoallylic alcohols, where there is ample opportunity for double bond migration and/or allylic oxidation, remains unexplored. In order to investigate the course of reaction we carried out a detailed study of PCC oxidation on homoallylic alcohols.

As shown in Table 3, oxidation of 3-methyl-3-buten-1-ol **4** with PCC (3 equiv.) gave 3-methyl-2-butenal **5** in 68% yield arising from alcohol oxidation and subsequent double bond migration. However oxidation of homoallylic alcohol **6** with PCC (3 equiv.) afforded a mixture of **7** and **8** (1:1) in 60% yield. Presumably, the reaction proceeded initially by the oxidation of alcohol followed by double bond migration to give **7** and subsequent allylic/benzylic oxidation furnished compound **8**. Similarly, the oxidation of **9** resulted in isomerization of *cis*- to the *trans*-olefin eventually leading to a mixture of compounds **10** and **11** in a 1:1 ratio. The oxidation of long chain aliphatic *cis*-homoallylic alcohols gave the products arising from alcohol oxidation, double bond migration with concomitant isomerization of the *cis*- to the *trans*-olefin and allylic oxidation (entries 4–7). When the concentration of PCC was lowered from 3 to 1.5 equiv. (entry 7) a mixture of **15**[8] and **18** was obtained. Thus, a useful one-pot conversion of homoallylic alcohols to 1,4-dicarbonyl-2*E*-ene compounds was achieved with PCC.

To summarize, we have explored a new and novel oxidation reaction by PCC involving C–C bond cleavage during oxidation of homobenzylic alcohol to benzylic aldehyde or ketone. This is one of the rare reactions of PCC where a degradation of one carbon occurs and yet the end product remains an aldehyde or ketone without further oxidation. Such a reaction will be very useful in analyzing functional group compatibilities in designing oxidation reactions involving PCC. On the other hand, homoallylic alcohols produced quite interesting results due to double bond migration, concomitant *cis*- to *trans*-isomerization and/or allylic oxidation. Thus, this investigation led to the useful one-pot conversion of homoallylic alcohols to 1,4-dicarbonyl-2*E*-ene compounds that may have potential as intermediates in organic synthesis. Therefore, the results described above may have a major impact on the application of PCC oxidation in synthetic organic chemistry.

Table 3. PCC oxidation of homoallylic alcohols[7]



Entry	Substrate	Eq. of PCC	React. time/h	Product	Yield %
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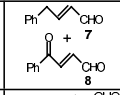
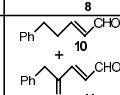
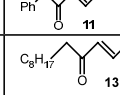
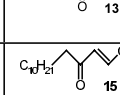
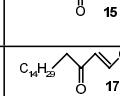
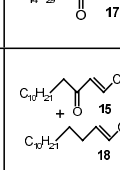
2		3	8		1:1 60[a]
3		3	8		1:1 58[a]
4		3	8		58
5		3	8		59[8]
6		3	8		60
7		1.5	8		30 28

[a]yields refer to the mixture of **A** and **B**

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7. **General procedure**: To a mixture of PCC (1.5 or 3–4 equiv.) and powdered molecular sieves (3 Å, one-half the weight of PCC) in dry CH_2Cl_2 was added the homobenzylic or homoallylic alcohol (1 equiv.) at 0°C. The reaction mixture was stirred for the specified time (4–15 h) at room temperature. CH_2Cl_2 was evaporated and to the residue was added Et_2O. The slurry was stirred and filtered through a pad of Celite. The residue was washed 3–4 times with Et_2O and filtered. The filtrate was concentrated to give virtually pure carbonyl compounds. In Table 3, entry 7, the products **15** and **18** were separated by flash silica gel column chromatography.
8. **4-*oxo*-Pentadec-2*E*-enal (15)**: White solid; yield: 59%; mp 78–80°C; IR (neat, cm^{-1}): 2736, 1696, 1694, 1612, 1216, 759, 477; ^1H NMR (200 MHz, $CDCl_3$): δ 0.88 (t, $J=6$ Hz, 3H), 1.2–1.3 (m, 16H), 1.69 (m, 2H), 2.7 (t, $J=8$ Hz, 2H), 6.83 (m, 2H), 9.8 (d, $J=6$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.03, 22.64, 23.66, 29.07, 29.29, 29.55, 31.86, 41.20, 137.28, 144.89, 193.34, 200.14; EIMS (m/z relative intensity,%): 238 [M^+] (9.1), 209 [M^+–CHO] (68.2), 195 (3.2), 183 (4.5), 153 (5.8), 139 (28.6), 125 (43.5), 111 (15.6), 98 (56.5), 83 (76.6), 70 (40.2), 55 (100). Anal. calcd for $C_{15}H_{26}O_2$ (238.37): C, 75.58; H, 10.99. Found: C, 75.39; H, 10.76%.