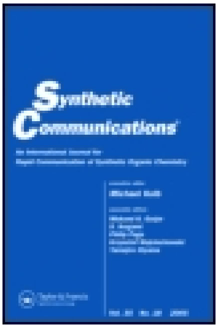

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OXIDATION OF CERTAIN 4-SUBSTITUTED PHENETHYL ALCOHOLS WITH COLLINS REAGENT: ON THE MECHANISM OF A CARBON-CARBON BOND CLEAVAGE

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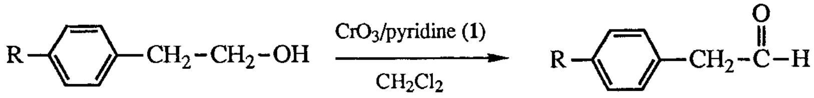
Abstract: A mechanism is proposed for a carbon-carbon bond cleavage observed in the oxidation of certain 4-substituted phenethyl alcohols with Collins reagent.

Oxidation of primary alcohols with Collins reagent (**1**) is a very important method for the preparation of aldehydes.[1-2] We required a variety of 4-substituted phenylacetaldehydes (**2**) as intermediates for the preparation of a series of compounds as potential serine protease inhibitors. As various 4-substituted phenethyl alcohols (**3**) have become commercially available, it appeared worth trying to synthesize the desired aldehydes (**2**) through oxidation of **3** by **1** (Scheme 1).



3 **2**

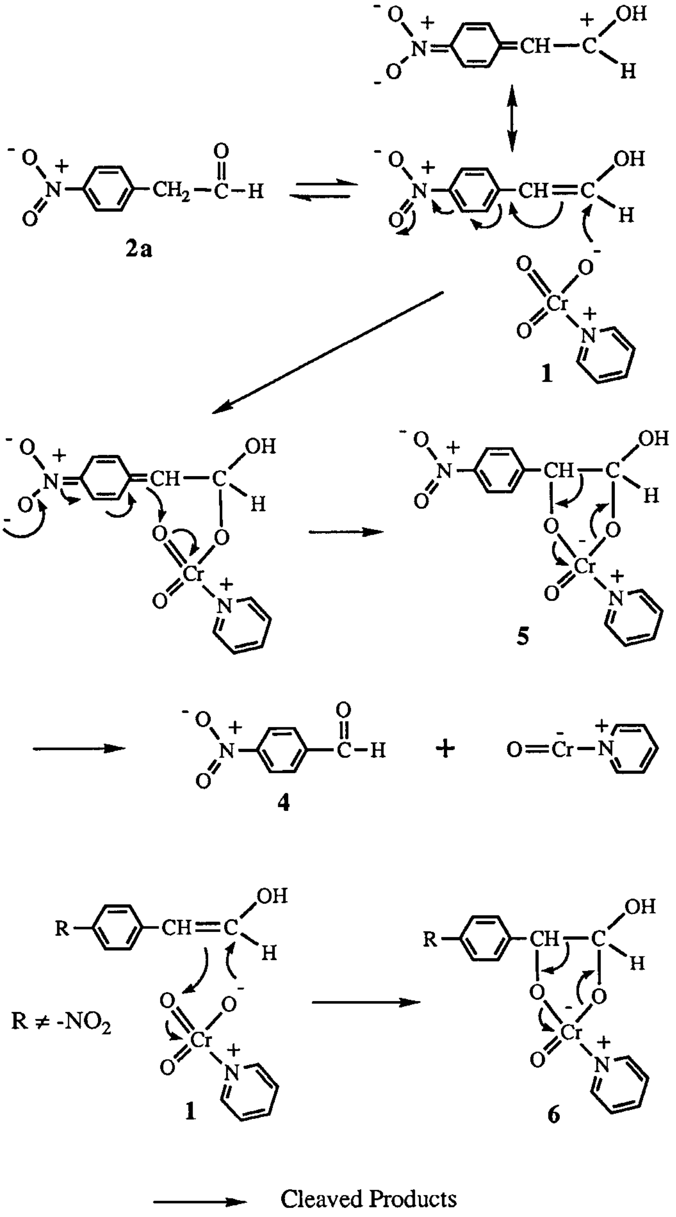
	R		R
a,	$-NO_2$;	**b**,	-OMe;
c,	-Cl;	**d**,	$-N(Me_2)$.

Scheme 1

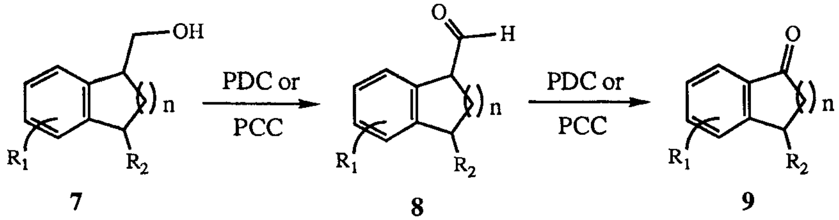
However, when **3a** was subjected to the modified oxidation procedure,[2] no desired product (**2a**) was obtained. Instead, 4-nitrobenzaldehyde (**4**) (~30%)[3] was obtained along with the recovered starting material **3a** (~70%). The unexpected formation of **4** can be rationalized in the mechanism proposed in Scheme 2. The desired product (**2a**) was probably formed initially, but was immediately attacked by another molecule of the reagent (**1**). Because of the resonance effect induced by the nitro group, such attack should be greatly facilitated to give the intermediate **5** as indicated in Scheme 2. The subsequent rearrangement ought to proceed efficiently as well, since no trace amount of **2a** could be detected in the final reaction mixture. Due to its central role in the proposed mechanism to retain the negative charge, replacement of the nitro group with other groups, such as methoxy or chloro, would implicate that the key cyclo intermediates (**6**) should be formed in a concerted way (Scheme 2). As such a direct pathway is probably energetically unfavorable, the aldehydes formed should be much less vulnerable towards attack by **1**. Indeed, when **3b** and **3c** were oxidized by **1**, the desired compounds **2b** and **2c** were formed in good to excellent yields,[4] while further degradation products (4-methoxy- and 4-chlorobenzaldehydes) were less than 5% (based on NMR data). Unexpectedly, no reaction occurred when **3d** was used as a substrate for the oxidation.

Recently, a similar C-C bond cleavage was observed when a series of compounds (**7**) were oxidized by using five molar excess of pyridinium dichromate (PDC) or pyridinium chlorochromate (PCC) (Scheme 3).[5] No detailed mechanism was offered to explain the cleavage, although evidence was provided that enolization of **8** was required for the subsequent cleavage.[5]

We believe that the mechanism proposed here can be applied to that case. The species responsible for the cleavage would be **10** and **11**, structurally similar to **1**. By examining the structural features of the compounds studied,[5] it is obvious

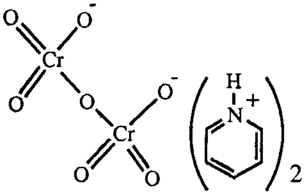


Scheme 2. Proposed Mechanism of Oxidative Cleavage

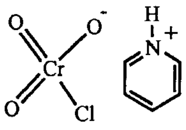


R_1 = -H, -Me, or -OMe;
R_2 = -H, -Me.
n = 1, 2.

Scheme 3



10, PDC



11, PCC

that the oxidation of these compounds (**7**) should behave more like that of **3b** and **3c**, rather than **3a**, i.e., formation of the cleaved compounds (**9**) from the initially formed aldehydes (**8**) would be very slow. This was indeed the case observed: after 5 h reaction, the initially formed aldehydes (**8**) were still present in approximately equal amounts with the compounds formed from the subsequent cleavage (**9**).[5]

Experimental

All chemicals were obtained from Aldrich Chemical Co. ^{1}H-NMR spectra were acquired on a Varian Associates XL-300 NMR spectrometer. Tetramethylsilane (TMS) was used as an internal reference in organic solvents. Mass spectra were obtained on a Finnigan MAT-90 mass spectrometer.

The modified procedure[2] of Collins oxidation was adopted for oxidation of the alcohols. The reaction mixtures, after diluted with excess ether, were worked up by washing with 5% NaOH, 5% HCl, and saturated $NaHCO_3$, respectively.

Acknowledgment

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2. Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000-4002.
3. The isolated product (by silica gel chromatography) was characterized by NMR and MS spectrometry and the data were found to be identical with that from an authentic sample: ^{1}H-NMR ($CDCl_3$) δ 10.17 (s, 1 H), 8.41 (d, 2 H, J = 8.7 Hz), 8.09 (d, 2 H, J = 8.7 Hz); EIMS m/z (relative intensity) 151 (M^+, 100), 150 (M^+ - H, 87), 105 (M^+ - NO_2, 23).
4. These two compounds (**2a** and **2b**) were previously synthesized by oxidation of the corresponding styrenes, using lead tetraacetate[a] and thallium (III) nitrate,[b] respectively. (a) Lethbridge, A.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc. Perkin I* **1973**, 35-38. (b) McKillop, A.; Hunt, J. D. *Tetrahedron Lett.* **1970**, *60*, 5275-5280.
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