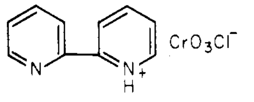
Communications

4-(Dimethylamino)pyridinium Chlorochromate, a New Selective Reagent for the Oxidation of Allylic and Benzylic Alcohols[1]

Summary: 4-(Dimethylamino)pyridinium chlorochromate (**3**) is a mild selective reagent for the oxidation of complex allylic and benzylic alcohols to the corresponding carbonyl compounds.

Sir: Chromium(VI) reagents have been widely used in organic chemistry for the oxidation of primary and secondary alcohols to carbonyl compounds.[2] Recently we reported on the usefulness in organic synthesis of two new Cr(VI) reagents—2,2′-bipyridinium chlorochromate (**1**) and 2,2′-bipyridine–chromium trioxide complex (**2**).[3] These



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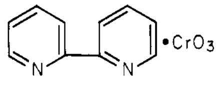
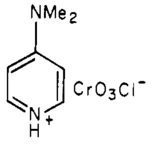


2

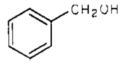
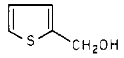
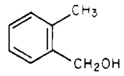
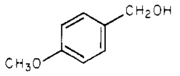
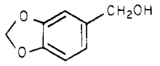
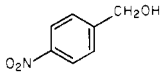
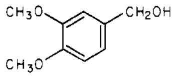
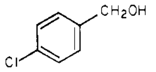
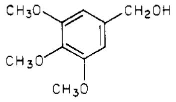
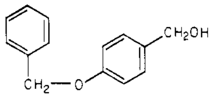
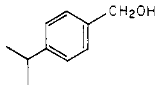
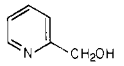
results indicated that synthetically useful changes in the properties and reactivity of chromium(VI) reagents could be brought about by varying the amine ligand associated with chromium trioxide. Of special interest to us was the moderate selectivity shown by **2** in the oxidation of allylic and benzylic alcohols. While this reagent is limited by some of the difficulties associated with Collins-type oxidations (long reaction times, large excesses or reagent required for successful oxidation),[2] we now report a new Cr(VI) reagent which enhances the selectivity of **2** while retaining the advantages of **1**: 4-(dimethylamino)pyridinium chlorochromate (**3**).



3

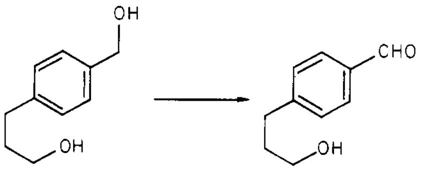
3 (DMAP·$HCrO_3Cl$)

Table I. Oxidation of Benzylic Alcohols to Aldehydes with DMAP·$HCrO_3Cl$

alcohol	conditions: equiv (time, h)[a]	% yield[b]
	3 (3)	64
	3 (4)	73
	4 (15)	78
	4 (6)	87
	5 (15)	98
	6 (20)	43
	4 (14)	91
	5 (21)	91
	3 (14)	86
	6 (15)	88
	4 (14)	72
	4 (6)	0

[a] Conditions not optimized. [b] Isolated yield of purified product.

The selectivity of this reagent was indicated by the remarkably slow oxidation of primary alcohols relative to allylic or benzylic alcohols, using DMAP·$HCrO_3Cl$. Treatment of *n*-heptanol with 4.0 equiv of **3** for 4 h leads to only 5% oxidation to *n*-heptanal; 94% of the alcohol can be recovered intact. Under similar conditions high yields of aldehydes are obtained from the corresponding benzylic and allylic alcohols (Tables I and II).[4] This contrast in behavior led us also to investigate the utility of DMAP·$HCrO_3Cl$ in selective oxidation of polyols and sensitive allylic alcohols. The oxidation of 3-[4-(hydroxymethyl)phenyl]propanol (**4**) is especially illustrative of the reagent's selectivity. Treatment of this diol with 4.0 equiv of DMAP·$HCrO_3Cl$ in dichloromethane for 2 h selectively afforded benzylic aldehyde **5** in 62% yield. Less than 2% of the corresponding dialdehyde was formed under these conditions. In contrast, under normal reaction conditions the widely used pyridinium chlorochromate[2c] (1.5 equiv, 20 min) afforded a mixture containing **5** and dialdehyde in yields of 45% and 32%, respectively.



4 **5**

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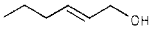
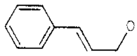
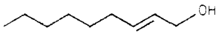
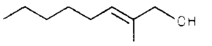
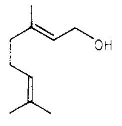
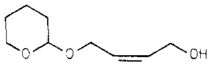
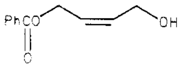
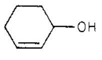
[1] Presented in part at the 11th Northeast Regional Meeting of the American Chemical Society, Rochester, NY, Oct 1981.

[2] (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: New York, 1972; pp 257–258 and references therein. (b) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1968**, 3363. (c) Corey, E. J.; Suggs, J. W. *Ibid.* 2647 (1975).

[3] Guziec, F. S., Jr.; Luzzio, F. A. *Synthesis* **1980**, 691.

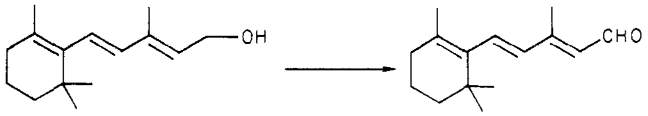
[4] Reported yields are those of isolated products. Expected spectral data obtained for all compounds. Satisfactory combustion analyses were obtained for all new compounds.

Table II. Oxidation of Allylic Alcohols to Aldehydes with DMAP·HCrO$_3$Cl

alcohol	conditions: equiv (time, h)[a]	% yield[b]
	6 (16)	42
	6 (15)	62
	6 (24)	90
	6 (12)	72
	4 (10) 6 (15)	73[c] 88[c]
	5 (24)	55[d]
	4 (24)	75[d]
	6 (7)	74

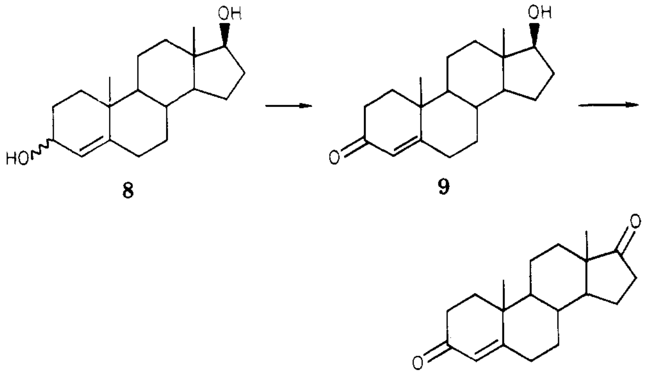
[a] Conditions not optimized. [b] Isolated yield of purified product. [c] Product is geranial; no neral could be detected. [d] Isomerized completely to *E* aldehyde.

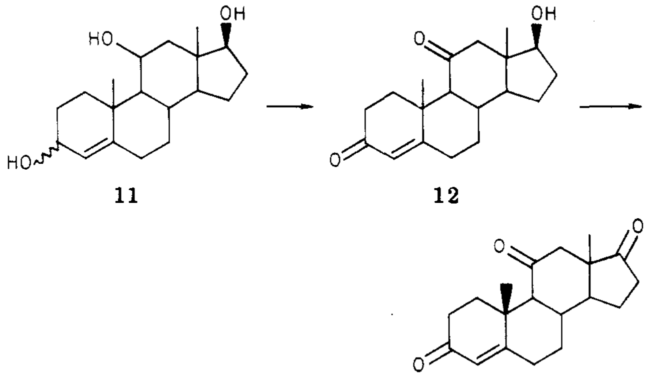
Oxidation of the extremely sensitive vitamin A intermediate (**6**) with 4.5 equiv of **3** in dichloromethane for 2 h afforded aldehyde **7** in 26% isolated yield. Aside from the aldehyde only unreacted alcohol (19%) could be recovered from the reaction mixture. Longer reaction times led only to decreased yields of aldehyde **7**. Oxidation of geraniol (Table II) afforded geranial in high yield with no observed isomerization to neral.


6 7

Secondary alcohols proved to be more reactive toward DMAP·HCrO$_3$Cl than primary alcohols. Treatment of 2-heptanol with 4.0 equiv of **3** for 5.0 h affords 2-heptanone in 16% yield (83% recovered alcohol). Under identical conditions cyclopentanol was converted to cyclopentanone in 22% yield (78% recovered alcohol). Still, benzylic and allylic alcohols proved to be significantly more reactive and moderate selectivity upon oxidation of complex diols was expected.

The diol reduction product **3** of testosterone[6] could be oxidized to testosterone **9** in 44% yield, using DMAP·HCrO$_3$Cl (4 equiv, 6 h). Under these conditions dione **10** was also isolated in 11% yield. Increasing the reaction time to 36 h led to decreased selectivity, affording **9** and **10** in yields of 23% and 17%, respectively. Approximately equal amounts of **9** and **10** were obtained upon oxidation of **8** with pyridinium chlorochromate[2c] (1.5 equiv). Oxidation of the reduction product (**1**) of andrenosterone[7] with 3 equiv of DMAP·HCrO$_3$Cl for 4 h in dichloromethane afforded 11-oxotestosterone (**12**) in 49% yield. Less than 3% of the trione andrenosterone (**13**) was formed under these conditions.


8 9 10


11 12 13

4-(Dimethylamino)pyridinium chlorochromate (**3**) is a nonhygroscopic shelf-stable crystalline solid which can be easily prepared. 4-(Dimethylamino)pyridine (4.00 g, 32.8 mmol) was added to an ice-cold, vigorously stirred solution of chromium trioxide (3.27 g, 32.7 mmol) in 20 mL of 1.65 M aqueous hydrochloric acid, affording a thick yellow-orange slurry which was stirred in an ice bath for an additional 30 min. The resulting yellow-orange solid was collected on a sintered glass funnel and washed with two 10-mL portions of ice-cold distilled water, kept under suction until moderately dry, and placed under vacuum pump pressure until a dry powder. This reagent is moderately light sensitive and should be protected from light during preparation and storage.[8] Yields of 90–92% of **3** have been routinely obtained with this procedure.

In the normal procedure the alcohol (4–7 mmol) was added in one portion with stirring to a 4–6-fold excess of DMAP·HCrO$_3$Cl in dichloromethane (20 mL). After being stirred for 15 h the mixture was diluted with ether (petroleum ether for allylic alcohol oxidation) and the powdery brown chromium reduction products were removed by filtration through Celite. Typically no 4-(dimethylamino)pyridine is observed in the crude filtrate. Direct Kugelrohr distillation for sensitive products, or washing with 2 N hydrochloric acid, followed by dilute sodium carbonate wash, drying, and distillation or crystallization completed the workup.

It should be noted that reagent **3** is acidic enough to isomerize initially formed *Z* unsaturated aldehydes to the corresponding *E* isomers (Table II). It is also worth noting that throughout this investigation only one compound—2-pyridylcarbinol—behaved in an anomalous manner. Normal reaction conditions led to a vigorous exothemic

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(5) Wendler, N. L.; Slates, H. L.; Tishler, M. *J. Am. Chem. Soc.* **1949**, *71*, 3267. Wendler, N. L; Slares, H. L.; Trenner, N. R.; Tishler, M. *Ibid.* **1951**, *73*, 719.

(6) Butenandt, A.; Heusner, A. *Ber. Dtsch. Chem. Ges.* **1938**, *71*, 202.

(7) Mancera, O.; Rosenkranz, G.; Sondheimer, F. *J. Chem. Soc.* **1953**, 2189.

(8) We have noticed a similar light sensitivity for both pyridinium chlorochromate[2c] and bipyridinium chlorochromate (1).[3]

reaction. No aldehyde could be isolated, but copious amounts of 4-(dimethylamino)pyridine were recovered upon workup, apparently due to ligand exchange.

Manganese dioxide has been widely used for the selective oxidation of allylic and benzylic alcohols. Unfortunately, this specially prepared reagent must be used in large excess, and long reaction times are often necessary for successful oxidations.[9] The recently described bis(tetrabutylammonium)dichromate[10] shows selectivity in benzylic and allylic oxidations, but workup is complicated and no details of oxidation of complex multifunctional molecules have been reported. The ready preparation of 4-(dimethylamino)pyridinium chlorochromate, its selectivity, and the ease of using this reagent indicate that **3** may prove to be a useful alternative to other reagents in oxidations of complex allylic and benzylic alcohols.[11] Investigations into the reasons for the observed selectivity and into the usefulness of other ligands in selective oxidations are currently in progress.[12]

Acknowledgment. We thank Reilly Tar and Chemical Corp. for providing 4-(dimethylamino)pyridine and Professor Paul Vouros for providing low-resolution mass spectra. We also gratefully acknowledge the helpful comments of Professor Harold Kwart.

Registry No. **3**, 81121-61-1; **4**, 38628-53-4; **5**, 81121-62-2; **6**, 3917-39-3; **7**, 3917-41-7; **8**, 81176-75-2; **9**, 58-22-0; **10**, 63-05-8; **11**, 81176-76-3; **12**, 564-35-2; benzyl alcohol, 100-51-6; 2-thiophenemethanol, 636-72-6; *o*-methylbenzyl alcohol, 89-95-2; *p*-methoxybenzyl alcohol, 105-13-5; 5-benzodioxolemethanol, 495-76-1; *p*-nitrobenzyl alcohol, 619-73-8; 3,4-dimethoxybenzyl alcohol, 93-03-8; *p*-chlorobenzyl alcohol, 873-76-7; 3,4,5-trimethoxybenzyl alcohol, 3840-31-1; *p*-(benzyloxy)benzyl alcohol, 836-43-1; *p*-isopropyl benzyl alcohol, 536-60-7; 2-pyridinemethanol, 586-98-1; hex-zen-1-ol, 928-95-0; 3-phenylprop-2en-1-ol, 4407-36-7; non-2-en-1-ol, 31502-14-4; 2-methyloct-2-en-1-ol, 33965-55-8; geraniol, 106-24-1; 4-(tetrahydropyranyloxy)-but-2-en-1-ol, 58201-77-7; 4-hydroxybut-2-enyl benzoate, 81121-63-3; 2-cyclohexen-1-ol, 822-67-3; benzaldehyde, 100-52-7; 2-thiophenecarboxaldehyde, 98-03-3; *o*-methylbenzaldehyde, 529-20-4; *p*-methoxybenzaldehyde, 123-11-5; 5-benzodioxolecarboxaldehyde, 120-57-0; *p*-nitrobenzaldehyde, 555-16-8; 3,4-dimethoxybenzaldehyde, 120-14-9; *p*-chlorobenzaldehyde, 104-88-1; 3,4,5-trimethoxybenzaldehyde, 86-81-7; *p*-(benzyloxy)benzaldehyde, 4397-53-9; *p*-isopropylbenzaldehyde, 122-03-2; 2-hexenal, 505-57-7; 3-phenyl-2-propenal, 104-55-2; 2-nonenal, 2463-53-8; 2-methyl-2-octenal, 73757-27-4; geranial, 141-27-5; 4-(tetrahydropyranyloxy)-2-butenal, 78008-26-1; 4-(benzyloxy)-2-butenal, 81121-64-4; 2-cyclohexenone, 930-68-7.

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[9] Reference 2a, pp 265–267.

[10] Santaniello, E.; Ferraboschi, P. *Synth. Commun.* **1980**, *10*, 75.

[11] For example, oxidations of compound **6** with manganese dioxide required very long reaction times, affording the aldehyde as a mixture of cis and trans isomers, often in low yield. Oxidation of geraniol with bis(tetrabutylammonium) dichromate affords a mixture of geranial and neral (9:1).

[12] It appears that chromate esters form in high yield even in the cases of primary and secondary alcohols and that differential breakdown of the chromate esters leads to the observed selectivity. Most simply, changing ligands on chromium changes its oxidation potential and, therefore, its reactivity.

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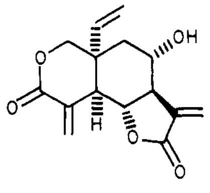
Stereocontrol in the Intramolecular Diels–Alder Reaction. 4. A Remarkable Effect of Overlap Requirements in the Connecting Chain[1]

Summary: The intramolecular Diels–Alder cyclizations of two triene diesters derived from (*E*)-3,5-hexadienoic acid have been investigated. The cyclizations proceed remarkably sluggishly and only after double-bond isomerization to the sorbate derivative has occurred. The reasons behind this unusual behavior were investigated, and evidence points strongly to the effects of overlap requirements of the ester linkage in the transition state as the major factor.

Sir: As part of a synthetic approach to cis bicyclic δ-lactones related to vernolepin (**1**), we had occasion to investigate the thermal cyclization of triene ester **2** which was readily prepared from (*E*)-3,5-hexadienoic acid (**3**)[2] and methyl 2-(hydroxymethyl)acrylate (**4**)[3] by coupling with DCC/py (1.02 equiv) in ether at 0 °C for 12 h (78% yield).



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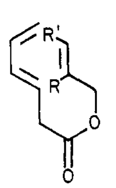
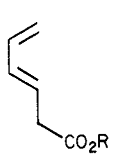
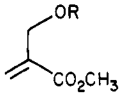


2, R = CO$_2$CH$_3$; R' = H
9, R = H; R' = CO$_2$C$_2$H$_5$



3, R = H
5, R = CH$_3$



4, R = H
6, R = Ac

However, in spite of the apparently good transition-state geometry for cycloaddition available to **2**,[4] thermolysis of **2** at a variety of temperatures up to 220 °C in high-boiling solvents in the presence of radical inhibitors afforded either recovery of **2** or polymeric products resulting from slow degradation of the dienophile segment in **2**.[5] To determine whether some inherent reactivity factor was preventing successful cycloaddition, we examined the analogous bimolecular reaction of methyl (*E*)-3,5-hexadienoate (**5**) and methyl (acetoxymethyl)acrylate (**6**). It was found that this bimolecular reaction occurred slowly but quite cleanly (110 °C/96 h) to afford a mixture of two δ-lactones **7** and **8** (2:1) after ring closure ((1) NaOCH$_3$/CH$_3$OH, room temperature, (2) 10% HCl/CH$_3$OH) in 70% yield. The structure and stereochemistry of **7** and **8** were established by correlation with authentic materials.[6] The surprising ease with which the bimolecular reaction took place suggested some significant energy barrier to cyclization was present in **2** as the result of electronic or steric interactions among the atoms in the connecting chain or of these atoms with the diene or dienophile segments of the substrate. The

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[1] Initial stages of these studies were conducted at Wayne State University, Detroit, Michigan.

[2] (a) Prepared in 69% yield by quenching the dianion prepared from sorbic acid (LDA (2.2 equiv) and HMPA in THF–hexane at 0 °C) with 6 N HCl; (b) J. B. Medwid, Ph.D. Dissertation, Wayne State University, Detroit, MI, 1980.

[3] Rosenthal, R. W.; Schwartzman, L. H.; Greco, N. P.; Proper, R. *J. Org. Chem.* **1963**, *28*, 2835.

[4] Examination of molecular models of **2**, focusing on the reacting centers, shows that good orbital overlap is possible at the appropriate trajectory angles of approach (75°) as judged from calculated values; E. Ciganek, private communication. We thank him for making his results available to us prior to publication.

[5] NMR spectra of the polymerized products suggested strongly that bimolecular Diels–Alder reactions were not the mechanism of polymerization. Diene resonances remained relatively intact; however, the characteristic methylene resonances of the dienophile were completely absent.

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