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OXYCHLORINATION OF ALKENES BY CHLOROCHROMATE REAGENTS: A FACILE PREPARATION OF α-CHLOROKETONES, AND COMPETITION BY SUBSTITUENT-DIRECTED OXIDATION.

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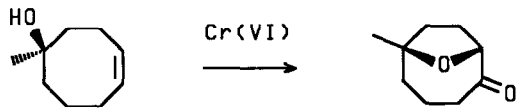
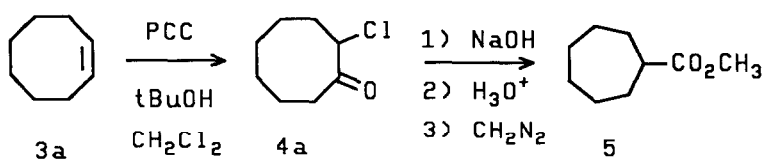
SUMMARY: *Cyanopyridinium chlorochromate effects a facile preparation of α-chloroketones from simple alkenes, cycloocta-1,5-diene and cyclododeca-1,5,9-triene; 1-methylcyclooct-4-en-1-ol undergoes oxidative cyclization.*

Several methods are available for the conversion of alkenes to α-chloroketones,[4] which are highly versatile synthetic intermediates.[5] Two of the standard reagents for this purpose, chromyl chloride and nitrosyl chloride, are less desirable for general use because of high volatility and toxicity, and a facile procedure is still wanting. In connection with our work on substituent-directed oxidation[6] and our interest in the relationship between selective oxidations and reagent structure, we have examined the reaction of some chromium(VI) reagent systems with several simple and multifunctional olefins, and we report a general α-chloroketone preparation.



1 2 [Eqn 1]

We have shown that 1-methylcyclooct-4-en-1-ol (1) undergoes a highly selective oxidative cyclization with pyridinium chlorochromate (PCC) to yield the ß-keto cyclic ether **2**, and we propose that this reaction proceeds by initial formation of a chromate ester followed by transannular attack of the bound oxidant on the alkene group.[6b] The importance of intramolecularity[7] in this transformation can be tested with appropriate intermolecular control reactions. To this end, a mixture of cyclooctene, **3a**, two equivalents of t-butanol and four equivalents of PCC in methylene chloride was heated to reflux over a period of two days. The reaction progress was monitored by tlc, and the alkene was slowly consumed with production of 2-chlorocyclooctanone,[4b,c,8] **4a**, isolated in 23% yield. In order to corroborate the structure, **4a** was subjected to the Favorskii reaction to give the ring contraction product, cycloheptanecarboxylic acid, which was isolated as the known[9] methyl ester **5** in 71% yield.



3a 4a 5 [Eqn 2]

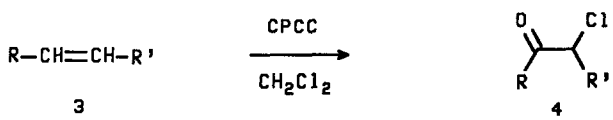
The presence of t-butanol is not essential to this transformation, and four to six equivalents of PCC at

reflux in methylene chloride gives a 20-40% isolated yield of **4a** after 2-3 days. Another variation tried was PCC in acetic acid at room temperature, which gives an approximately 50% yield of **4a** overnight. The more rapid conversion here suggests that a more acidic medium facilitates the reaction.

Corey has recently introduced 2-cyanopyridinium chlorochromate (CPCC) as a reagent for the selective 1,4-oxygenation of a cyclopentadiene.[10] Heterocycle-chlorochromate complexes show a trend where their strength as oxidants is inversely proportional to the donor strength of the heterocyclic ligand.[11] Enhanced reactivity is found for complexes containing a potential bidentate ligand which would require a small ring metallacycle for full coordination.[12] The pyridine nitrogen lone pair and the nitrile π-orbital of the 2-cyanopyridine may act in this regard. We have found that CPCC is the reagent of choice for the conversion of alkenes to α-chloroketones, and that this procedure seems to have broad applicability.

Representative examples are found in the Table. The reaction is generally complete in a matter of hours at room temperature, and the yields are good. An excess of oxidant is required for the best conversion; some optimization has been carried out for each substrate, and the values given represent the minimum amount of oxidant which gives complete consumption of starting material. The inclusion of Celite as an inert support during the reaction facilitates the workup, which consists of passing the crude reaction mixture through alumina, elution with an ether/petroleum ether mixture, and extraction with aqueous acid to remove cyanopyridine.

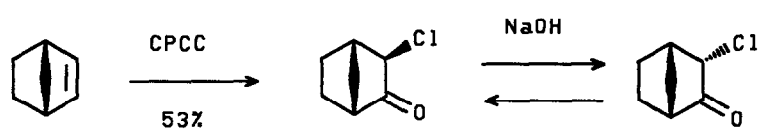
TABLE



3 4

Alkene		R	R'	equiv. CPCC	yield	refs.
3a		$-(CH_2)_6-$		11	**4a** 81%	4f,8
3b		nC_3H_7	nC_3H_7	7	**4b** 96%	13
3c		$-(CH_2)_5-$		8	**4c** 77%	13
3d	(E/Z)	$-(CH_2)_{10}-$		11	**4d** 79%	4b,14
3e	(Z,Z)	$-(CH_2)_2-CH=CH-(CH_2)_2-$		7	**4e** 58%	4f,15
3f		1,3-cyclopentadiyl		6	**4f** 53%	4b,16
3g	(Z,E,E)	$-(CH_2)_2-[-CH=CH-(CH_2)_2-]_2-$		6	**4g** 40%	17
3h	(E,E,E)	$-(CH_2)_2-[-CH=CH-(CH_2)_2-]_2-$		5	**4h** 38%	18

Cyclohexene reacts with CPCC to give in 70% yield a 5:1 mixture of 2-chlorocyclohexanone and cyclohex-2-one. This competitive allylic oxidation is more pronounced with PCC as the oxidant, but was not detected in the reactions of the other substrates; allylic oxidation is known to occur more easily in cyclohexenes.[18] Norbornene (**3f**) is cleanly oxidized to the known exo-**4f**; for structure confirmation, literature spectral data[16] were compared



[Eqn 3]

3f exo-4f endo-4f

with those of the product of base-catalyzed equilibration of exo-**4f** to a mixture of exo-**4f** and endo-**4f**.

Of special note is the conversion of the bifunctional substrate cycloocta-1,5-diene (**3e**) to 6-chlorocyclooct-1-en-5-one (**4e**) in reasonable yield. E,E,Z-Cyclododeca-1,5,9-triene (**3g**) is oxychlorinated to an approximately 1:1 mixture of E,Z and Z,E 1-chlorocyclododeca-5,9-dien-2-ones (**4g**) in 40% yield.[17] Thus, there is high selectivity for attack at one of the E-alkenes as is found for other such reactions of **3g**,[20] but there is no regioselectivity. E,E,E-Cyclododeca-1,5,9-triene (**3h**) furnishes E,E-1-chlorocyclododeca-5,9-dien-2-one (**4h**)[18] as a single product in 38% yield. The monoepoxides of **3g** and **3h** are also isolated as side products in this reaction; the intermediacy of an epoxide in this transformation is unlikely, since CPCC treatment of the epoxide of **3g** gives no reaction.

CPCC is a generally applicable oxychlorination reagent for alkenes. The question arises of its effect upon the bifunctional substrate **1**, and when employed in the reaction depicted in Eqn 1, two equivalents of CPCC effects the conversion **1** -> **2** in 26% yield, with no trace of the regioisomeric product.[6b] The high selectivity for **2** cannot be explained by initial oxychlorination. The substituent-directed oxidation involving the prior formation of a chromate ester must predominate, and the bound chromate is constrained to follow the oxyalkoxylation pathway which we have previously described.[6b]

The mechanism of this oxychlorination is likely quite similar to that for the reaction of chromyl chloride with alkenes.[4,21] A substantial amount of cyanopyridine is recovered in the crude product, and CPCC may generate chromyl chloride or a related species *in situ*. The CPCC system is more efficient in the production of α-chloroketone, since the reaction of **3f** with chromyl chloride gives the syn,exo-hydroxychloride as the major product.[4,16]

A typical procedure follows: *A suspension of 6.75 g of Celite in 60 mL of methylene chloride at room temperature is charged with 4.501 g of CPCC (18.7 mmol) and with 0.3 g of trans-oct-4-ene (**3b**, 2.67 mmol). This mixture is stirred for 3 h, and is then passed through a column of 30 g of alumina and eluted with a total of 300 mL of petroleum ether. The eluate is concentrated to 50 mL on a rotovap, and is then extracted three times with 5% $HCl_{(aq)}$. The organic layer is extracted with 50 mL of brine, dried ($MgSO_4$) and concentrated to yield 0.415 g of 5-chlorooctan-4-one,[13] (**4b**, 96%): IR (thin film) 1720 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.23 (dd, 1H, J = 6, 7.5 Hz).*

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