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OXIDATIVE CATIONIC CYCLIZATION REACTIONS EFFECTED BY PYRIDINIUM CHLOROCHROMATE

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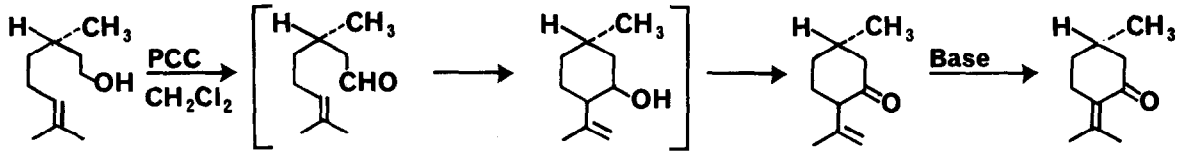
Pyridinium chlorochromate (PCC), $C_5H_5N^+HClCrO_3^-$, first introduced as an oxidizing reagent for alcohols just three years ago,[1] has found widespread use in organic synthesis.[2] In earlier work advantage was taken of the mildly acidic character of the reagent to bring about an essentially one-step conversion (70% yield) of (-)-citronellol (1) to (-)-pulegone (2),[3] a useful reagent for asymmetric synthesis of prostaglandins.[4] The effectiveness of this synthesis together with our interest in exploring new techniques for



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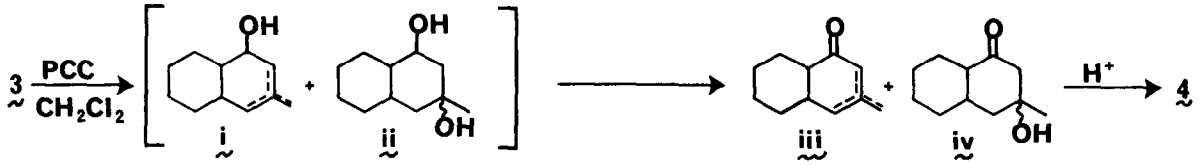
ring formation and annulation[5,6] provided incentive for a more detailed investigation of this oxidative cationic cyclization process. We report here the results of such a study and some conclusions with regard to scope and limitations.

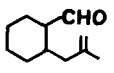
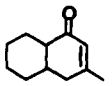
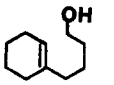
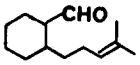
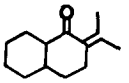
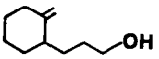
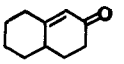
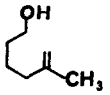
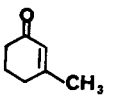
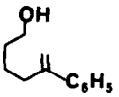
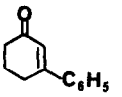
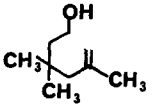
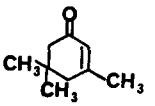
The utility of PCC for the annulation of cyclic unsaturated alcohols or aldehydes to form fused-ring cyclohexenones was of special interest since such enones could in principle be formed with the enone carbonyl either α- or β- to the fusion atoms and the C=C unit on either the fusion or non-fusion side of the carbonyl. Such flexibility is demonstrated by the results summarized in Table I (entries A-D).[7] In most of the cases cited in Table I the cyclization process, which is easily monitored by thin layer chromatography (tlc), leads to a number of detectible intermediates. In the cyclization of 3, for example, initial formation of the alcohols i and ii[7] can be observed as can be their further oxidative conversion to a mixture of the unsaturated ketones iii and the β-hydroxy ketone iv.[7] Treatment of the mixture of enones iii and the β-ketol iv with p-toluenesulfonic acid-benzene converted iii and iv to the desired conjugated enone 4. In general reaction products from oxidative cyclization were similarly treated with acid to effect the transformation of β,γ -enone and β-ketol components to α,β-enone as indicated in Table I.



i ii iii iv

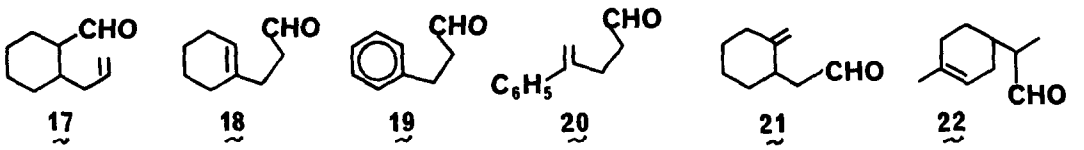
Efficient cyclization using the reagent PCC was only observed with substrates capable of affording a tertiary cation as the initial cyclic intermediate. Thus, substrate 17 failed to undergo appreciable

Table I. Oxidative Cationic Cyclization Reactions Effected by Pyridinium Chlorochromate

Entry	Substrate	Conditions[a]	Product[b]	% Yield
A	3[c] 	1. 3.0 equiv PCC, 4.5 hr. 2. TsOH	 4[d]	78%
B	5 	1. 5.0 equiv PCC, 42 hr. 2. TsOH	 6[e]	55%
C	7[f] 	1. 3.0 equiv PCC, 14.5 hr. 2. base	 8[g]	41%
D	9 	1. 5.0 equiv PCC, 7 hr. 2. TsOH	 10[h,i]	62%
E	11 	1. 5.0 equiv PCC, 22 hr. 2. TsOH	 12[i]	68%
F	13 	1. 4.0 equiv PCC, 16 hr. 2. TsOH	 14[i,j]	69%
G	15 	1. 5.0 equiv PCC, 24 hr. 2. TsOH	 16[i]	65%

(a) Dry methylene chloride (CH_2Cl_2, 6-10 ml/mmol substrate) as solvent for the oxidative cationic cyclization sequence conducted at 20-23° C. Acid treatment, p-toluenesulfonic acid (TsOH, 10-20 mg/mmol), of the crude oxidative cationic cyclization products was carried out in refluxing benzene (5-8 ml/mmol, 1-1.5 hr); base treatment is 5.0 ml of 0.05 N NaOH/EtOH per mmol, 50°, 1 hr. (b) See ref. 7. (c) Mixture of ca. 1/1 cis/trans isomers. (d) Identical in all respects with authentic material, 2,4-DNP mp 198.5-200° (lit. mp 201-202°, ref. 10). (e) 2,4 DNP mp 264-265° (lit. mp 264-265°, ref. 9b). (f) Mixture of ca. 2/3 cis/trans isomers. (g) Mixture of ca. 1/1 cis/trans isomers. (h) Contains ca. 5% of the non-conjugated $\Delta^{9,10}$-2-octalone, see ref. 11. (i) Identical in all respects with authentic material. (j) Mp 63-64° (lit. mp 64-65°, ref. 12).

cyclization under the conditions outlined in Table I or even under more forcing circumstances, in contrast to the closely related case 3 → 4. This requirement for proper substitution and nucleophilicity at the carbon-carbon double bond represents a well-defined limitation on the scope of PCC induced cyclization. Another restriction was observed with respect to the size of the ring created in the cyclization. All attempts to form 5-membered, i.e., cyclopentenone, structures were to no avail using as substrates the aldehydes 18-22, even under more forcing conditions involving the addition of strong acids (e.g., CF_3CO_2H, CH_3SO_3H) to the PCC reagent. Analogous observations[8] have been made regarding the failure of other internal cation-olefin systems to generate 5-membered rings.



17 18 19 20 21 22

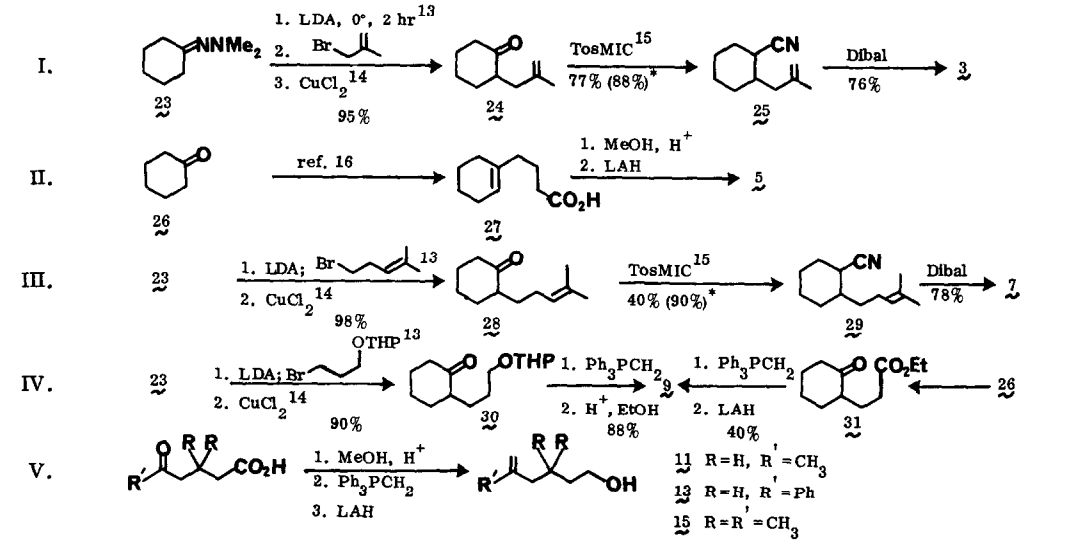
On the other hand entries E-G (Table I) illustrate that ring closure occurs smoothly with aliphatic substrates to form monocyclic products although the reaction rates are slightly slower than those for the formation of analogous ring-fused cyclohexenones (compare entries A-D).

The data in Table I illustrate that the oxidative cationic cyclization process employing PCC as both the oxidant and acid catalyst constitutes an easily monitored and effective method for the preparation of β,β-disubstituted α,β-unsaturated cyclohexenones. This process is both milder and more efficient than related cationic cyclizations employed for the preparation of α,β unsaturated enones.[6e, 8, 9] For instance, stannic chloride fails to catalyze cyclization of the unsaturated nitrile 25 (CH_2Cl_2, 25°).[8] Also, while our new process complements the aldol cyclization (Table I, entries D-G), it provides access to systems not readily obtainable through the aldol condensation (entries A-C; for instance, 2-acetonyl-1-acetyl cyclohexane affords a mixture of 4 and the isomeric 1-methyl-Δ^2-3-octalone upon aldol condensation[10]).

The methods of preparation of the substrates for the cyclization experiments (as outlined in Table I) are shown in Table II.

Table II. Preparation of Substrates

Scheme



( )* Yield based on recovered starting material.

The following experimental procedure is representative.[17]

3-Methyl-Δ^2-1-octalone (4) [1(4H)-Naphthalenone, 4a,5,6,7,8,8a-hexahydro-3-methyl]. Pyridinium chlorochromate[1] (862 mg, 4.0 mmol, 3.0 equiv) was added to a magnetically stirred solution of the unsaturated aldehyde 3 (222 mg, 1.34 mmol) in 9 ml of dry CH_2Cl_2. After 4.5 hr at 20° the solution was diluted with ca. 15 ml of dry ether and the supernatant liquid was passed through a short pad of Florisil using fresh ether to wash the insoluble black residue and Florisil pad. The crude product, after removal of the solvent under reduced pressure, was placed in 7 ml of dry benzene, p-toluenesulfonic acid (TsOH, 20 mg) was added and the resulting solution was refluxed for 1.5 hr. Isolation of the crude product by standard extractive workup followed by chromatography (15 g SiO_2, 15 x 1.5 cm, 25% ether:pet. ether eluant) afforded 170 mg (78%) of pure 4 homogeneous by glc, R_f=0.50[2] (ether:hex 1:1, SiO_2) identical in all respects with authentic material.[10] Pmr ($CDCl_3$, ppm): 5.82 (1H, broadened s, olefinic), 1.92 (3H, s, methyl); ir (film, cm^{-1}): 3020 (weak), 2915, 2850, 1670, 1635, 1450, 1435, 1427, 1380, 1245, 1208, 1168, 870; ms: 164 (M^+), 82 (base); 2,4-DNP mp 198.5-200° (lit. mp[10] 201-202°); ms: 344 (M^+, base).

References and Notes

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