Notes

Use of Pyridinium Chlorochromate as Methylene Oxidant in 5,6-Dihydropyrans: A Practical, One-Step Preparation of the Anhydromevalonolactone

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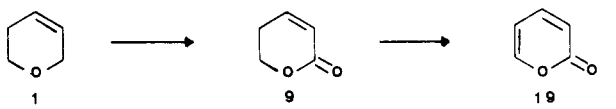
Since its first appearance,[1] PCC (pyridinium chlorochromate) has received much attention by synthetic chemists, because of its exceptional versatility as oxidizing agent in many usual and unusual situations.[2] So far no attempts have been made to oxidize methylene groups with PCC. On the other hand, allylic oxidation (SeO_2,[3] CrO_3, and derivatives[4]) or ether oxidation (RuO_4 and CrO_3[5]) are well-known. Of course, in more sensitive substrates, like allylic ethers, these reagents are much less useful for synthetic purposes and the only example known of such oxidation is that with SeO_2.[3a] Our purpose was to test PCC with substrates having an activated methylene group. Here we report the first example of oxidation of cycloallylic ethers such as 5,6-dihydropyrans, which leads in a single step to the corresponding α,β-unsaturated δ-lactones. The results obtained are collected in Table I.[6]

In a typical procedure the 5,6-dihydropyran (1 equiv) is stirred in a tightly capped bottle with anhydrous CH_2Cl_2, adding 3 equiv of PCC (freshly prepared) in three portions. The reaction is carried out at 60–70 °C[7] and can be easily followed by TLC or GC. After 8–24 h (with the exception of compounds **7** and **8**) the reaction is stopped and the mixture is poured into the top of silica gel column, chromatographed, and the product purified by distillation if necessary.

Note that yields range from good to excellent (the only exceptions being compounds **7** and **8**, discussed below), that the reaction conditions are mild, and that the procedure is simple. Other important features of the reaction are the absence of byproducts and easy recoverability of unreacted starting material.

Scheme I



Some of the examples in Table I are of special significance for the synthesis of natural products. Of particular importance is compound **10**, known as anhydromevalonolactone, which has been used as key material for the synthesis of pheromones[8] and of verrucarinic acid.[9] The methods described for the preparation of this compound employed either a three-step sequence with an overall yield of 71%[8,9a] or 80%[10,11] or a two-step sequence but with very low yield.[9b] In our sequence we use, as starting material, compound **2**, which is a relatively cheap commercial product (Aldrich). Anhydromevalonolactone **10** is obtained from **2** in one step in 85% yield. Direct oxidation of **2** to **10** has been attempted several times, as demonstrated by a number of patents,[12] but the methods used (CrO_3/Py, O_2 in the presence of transition-metal salts or complexes) and the reported yields (34–37%) do not compare favorably with our procedure.

Compound **9** also represents a key intermediate for the synthesis of verrucarinic acid.[9b] Furthermore, **9** is an intermediate for the synthesis of α-pyrone **19**, which is a commercially available product (Fluka)[13,14] (Scheme I).

The behavior of compounds **7** and **8** differs from the other compounds examined. Compounds **7** and **8**, which afford the oxidation products **15** and **17** in low yield and only after a prolonged reaction time, also give rise to the formation of the γ-dihydropyrones **16** and **18**. The decreased reactivity toward PCC of the above substrates may be traced back to the presence in both **7** and **8** of an allylic

(1) Corey, E. J.; Suggs J. W. *Tetrahedron Lett.* **1975**, 2647.

(2) See review: Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245–258.

(3) (a) Rabjohn, N. *Org. React. (N.Y.)* **1976**, *24*, 261. (b) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(4) See: Wiberg, K. B. "Oxidation in Organic Chemistry"; Accademic New York, Press: 1965; Part A, p 69.

(5) Lee, D. G. "Oxidation"; Augustine, Ed.; Marcel Dekker: New York, 1969; Vol. I, p 54 and 55.

(6) Starting materials such as compounds **1**, **3**, **7**, and **8** were prepared by literature methods. Compounds **2** and **6** are commercially available products (Aldrich). The lactones **9**, **10**, and **14** gave satisfactory IR, ^1H NMR, and mass spectra all in accordance with the literature data. Compounds **4**, **5**, and **11–18** are fully characterized in the Experimental Section.

(7) The reaction seems to be much slower at room temperature or at 35–40 °C; no attempts have been made at higher temperature because of the satisfactory results obtained at 60–70 °C.

(8) (a) For several examples and references, see: Mori, K. "The Total Synthesis of Natural Products"; ApSimon, Ed.; Wiley-Interscience: New York, 1982; Vol. 4, p 80, 81 and 86. (b) White, J. D.; Avery, M. A.; Carter, J. P. *J. Am. Chem. Soc.* **1982**, *104*, 5486.

(9) (a) White, J. D.; Carter, J. P.; Kazar, H. S., III *J. Org. Chem.* **1982**, *47*, 929. (b) Herold, P.; Mohr, P.; Tamm, C. *Helv. Chim. Acta* **1983**, *66*, 744.

(10) Gueldner, R. C.; Thompson, A. C.; Hedin, P. A. *J. Org. Chem.* **1972**, *37*, 1854.

(11) The reported yields of 71% (ref 9a) and 80% (ref 10) do not consider the preparation of the starting materials (4-hydroxy-2-butenone or 4-acetoxy-2-butenone, respectively), which are not commercially available, and can be obtained with the best method found in the literature (see: Tatsuo, A.; Makoto, I.; Kazuharu, Y.; Masafumi, H.; Masaru, K.; Kazuo, O. (Maruzen Oil Co., Ltd.) Japan Kokai 74 86 315, Aug 19, 1974; *Chem. Abstr.* **1975**, *82*, 139352c.) with a yield of 81%. Thus the exact overall yields for the preparation of anhydromevalonolactone **10** must be considered 58% for ref 9a and 65% for ref 10.

(12) Kyo, S.; Yasui, A. (Kuraray Co., Ltd.) Japan Kokai 72 48 386, Dec 16, 1972; *Chem. Abstr.* **1973**, *78*, 97481d. Oka, M.; Fujiwara, Y.; Itoi, K. (Kuraray Co., Ltd.) Japan Kokai 75 151 810, Dec 6, 1975; *Chem. Abstr.* **1976**, *84*, 164608o, Kyo, S.; Senoo, K.; Yamada, O. (Kuraray Co., Ltd.) Japan Kokai 76 13 776, Feb 3, 1976; *Chem. Abstr.* **1976**, *85*, 32842x.

(13) Nakagawa, M; Tomozuka, M.; Obi, M.; Kinchi, M.; Hino, T. *Synthesis* **1974**, 510.

(14) Compound **1** has been prepared by literature methods (Colonge, J; Boisde, P. *Bull. Soc. Chim. Fr.* **1956**, 824) with an improved yield of 60%, thus the overall yield of the three-step sequence to compound **9** is 45% with respect to the 32–37% yield reported for the direct preparation of **9** (ref 13).

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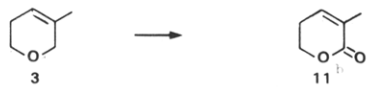
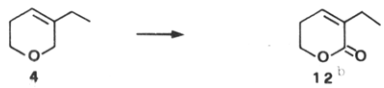
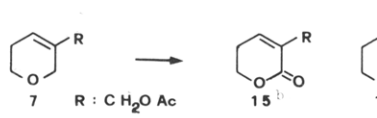
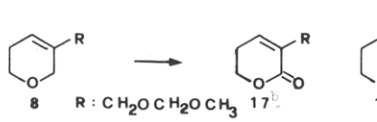
Table I. Reaction of 5,6-Dihydropyrans with PCC

5,6-dihydropyrans	products	yield,[a] %	reaction time, h
 1	9	70	7
 2	10	85	9
 3	11[b]	70	12
 4	12[b]	60	24
 5[b]	13[b]	70	24
 6	14	80	24
 7 R : CH_2OAc	15[b] 16[b] (2:1)	37	48
 8 R : $CH_2OCH_2OCH_3$	17[b] 18[b] (2:1)	37	48

[a] Determined by isolation. [b] Satisfactory elemental analyses have been obtained for all the new compounds listed in the table.

electron-withdrawing group.

In conclusion, the present method extends the use of PCC to the oxidation of activated methylene groups in sensitive substrates like 5,6-dihydropyrans, with several advantages over other oxidizing agents. Mild reaction conditions and good yields are noteworthy features of the method. Preliminary studies on related linear or five-membered ring allylic ethers give interesting but often different results.

Experimental Section

Melting points are uncorrected. Column chromatography was done on a silica gel 60, 70–230 mesh, and TLC on silica gel plates 60 (F_{254} Merck). ^1H NMR spectra were recorded on a Varian MA-360 (60 MHz) spectrometer with Me_4Si as internal standard. IR spectra were run on a Perkin-Elmer Model 298 spectrometer. Low-resolution mass spectra were run on a AEI-MS12 (70 eV) spectrometer. GC analyses were carried out on a HP 5880A instrument (FID) by using a 20-m-long capillary column (OV-101). Preparative HPLC separations were performed with a Waters Associates pump and dual cell refractometer detector, using a μ-Porasil Waters Associates column.

Preparation of Compounds 4 and 5. To a solution of 2.24 g (20 mmol) of $(CH_3)_3COK$ in anhydrous Me_2SO stirred in a two-necked flask at 0 °C was added dropwise 1.46 g (10 mmol) of 3-ethyl-4-chlorotetrahydropyran.[14] After 3 h at room temperatures, ice and 6 N HCl were added to the solution until pH 7 was reached. Then the mixture was extracted (two times) with *n*-pentane, and the organic phase was dried over anhydrous Na_2SO_4 and carefully evaporated in vacuo, giving a residue of 1.10 g (98%). The GC analysis of the mixture showed the presence of two reaction products. Separation by HPLC (hexane–acetate (95:5) as eluent) led to the two dihydropyrans **4** and **5** (2:1 ratio) characterized as follows.

Compound 4 (oil, bp 90 °C at atmospheric pressure): NMR ($CDCl_3$) δ 5.4 (1 H, cm), 4.0 (2 H, bs), 3.71 (2 H, t, J = 7 Hz); 1.7–2.3 (4 H, cm), 1.01 (3 H, t, J = 7 Hz).

Compound 5 (oil, bp 95 °C at atmospheric pressure): NMR ($CDCl_3$) δ 5.5–5.7 (2 H, cm), 4.02 (2 H, bs), 3.4–3.7 (2 H, cm), 2.0–2.3 (1 H, cm), 1.2–1.5 (2 H, cm), 1.10 (3 H, t, J = 7 Hz).

General Oxidation Procedure. The 5,6-dihydropyran (1 equiv) is added to a tightly capped bottle (with a stirring apparatus) in anhydrous CH_2Cl_2 (freshly distillated from P_2O_5). To the solution is added 1 equiv of PCC, and the mixture is stirred at 60–70 °C. Over a few hours, two other portions of PCC (2 equiv) were added to the mixture. The reaction can be followed by TLC (hexane–ether (1:1) as eluent). After several hours (see reaction times on Table I), the reaction is stopped and the cooled mixture is added to a silica gel column. Generally the column is eluted with hexane–ether (1:1); the residue starting material (higher R_f) and the final products (lower R_f) are easily separated and collected. Satisfactory elemental analyses were obtained for the new compounds (see Table I, footnote b).

Compound 11 (oil, bp 141 °C at 15 mbar): NMR (CCl_4) δ 6.52 (1 H, cm), 4.30 (2 H, t, J = 6 Hz), 2.2–2.6 (2 H, cm), 1.9 (3 H, m); IR (CCl_4) 1730, 1625 cm^{-1}; mass spectrum, m/z 112 (M^+), 82, 67, 54, 44.

Compound 12 (oil, bp 85 °C at 0.13 mbar): NMR (CCl_4) δ 6.38 (1 H, cm), 4.20 (2 H, t, J = 6 Hz), 2.0–2.4 (4 H, cm), 1.06 (3 H, t, J = 7 Hz); IR (CCl_4) 1730, 1640 cm^{-1}; mass spectrum, m/z 126 (M^+), 81, 67, 53.

Compound 13 (oil, bp 82 °C at 0.13 mbar): NMR (CCl_4) δ 6.65 (1 H, dd, J = 4, 10 Hz), 5.67 (1 H, d, J = 10 Hz), 4.1–4.5 (2 H, m), 2.2–2.6 (1 H, m), 1.5–1.7 (2 H, m), 1.0 (3 H, bt, J = 7 Hz); IR (CCl_4) 1740 cm^{-1}; mass spectrum, m/z 126 (M^+), 81, 67, 53.

Compound 15 (white solid, mp 53–54 °C): NMR ($CDCl_3$) δ 6.93 (1 H, m), 4.80 (2 H, m), 4.40 (2 H, t, J = 6 Hz), 2.3–2.7 (2 H, cm), 2.15 (3 H, s); IR ($CHCl_3$) 1740, 1720, 1650 cm^{-1}; mass spectrum, m/z 170 (M^+), 128, 127, 110, 82.

Compound 16 (white solid, mp 41–42 °C): NMR ($CDCl_3$) δ 7.58 (1 H, s), 4.68 (2 H, s), 4.52 (2 H, t, J = 6 Hz), 2.65 (2 H, t, J = 6 Hz), 2.02 (3 H, s); IR (CCl_4) 1730, 1675, 1620 cm^{-1}; mass spectrum, m/z 170 (M^+), 127, 111, 83, 43.

Compound 17 (oil bp 118–119 °C at 0.1 mbar): NMR (CCl_4) δ 6.70 (1 H, m), 4.52 (2 H, s), 4.27 (2 H, t, J = 6 Hz), 4.10 (2 H, m), 3.25 (3 H, s), 2.2–2.7 (2 H, cm); IR (CCl_4) 1730, 1625 cm^{-1}; mass spectrum, m/z 141 (M^+ – 31), 127, 112, 45.

Compound 18 (oil, bp 97–98 °C at 0.05 mbar): NMR (CCl_4) δ 7.20 (1 H, s), 4.47 (2 H, s), 4.40 (2 H, t, J = 6 Hz), 4.0 (2 H, s), 3.26 (3 H, s), 2.5 (2 H, t, J = 6 Hz); IR (CCl_4) 1730, 1685, 1625 cm^{-1}; mass spectrum, m/z 141 (M^+ – 31), 127, 112, 83, 45.

Registry No. 1, 3174-74-1; 2, 16302-35-5; 3, 29687-18-1; 4, 88981-46-8; 5, 88981-47-9; 6, 493-05-0; 7, 88981-48-0; 8, 88981-49-1; 9, 3393-45-1; 10, 2381-87-5; 11, 72649-02-6; 12, 85287-76-9; 13, 88981-50-4; 14, 4702-34-5; 15, 88981-51-5; 16, 88981-52-6; 17, 88981-53-7; 18, 88981-54-8; PCC, 26299-14-9; 3-ethyl-4-chlorotetrahydropyran, 35952-04-6.

Stereochemistry of the $HCuX_2$-Induced Formation of 1-Halo-3-phenylpropadienes from 1-Phenyl-2-propyn-1-ol and Some of Its Derivatives

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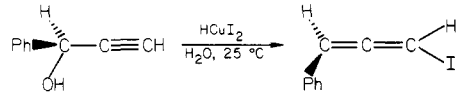
The lithium and tetrabutylammonium dihalocuprate induced conversions of 2-propynylic methanesulfonates,[1,2] methanesulfinates,[2] and chlorides[3] into 1-haloallenes proceed with high anti stereoselectivity. On the other hand, syn stereoselectivity has been observed for the $HCuBr_2$-induced conversion of a propargylic alcohol into the corresponding 1-bromoallene.[4] In this context it was of interest to know whether the syn stereoselectivity is a general feature of the $HCuX_2$-mediated 1-haloallene formation. It will be shown in this paper that this is not the case.

For our study we used (*R*)-(–)-1-phenyl-2-propyn-1-ol (**1a**), a compound that is readily available in optically pure form.[5] Treatment of optically pure (*R*)-(–)-**1a** with 1.0 equiv of $HCuI_2$—prepared by mixing equimolar amounts of CuI and HI with water as solvent—produced, after a 5 min reaction time at 25 °C, nearly quantitatively the 1-iodoallene **2a** (eq 1). The allene was dextrorotatory



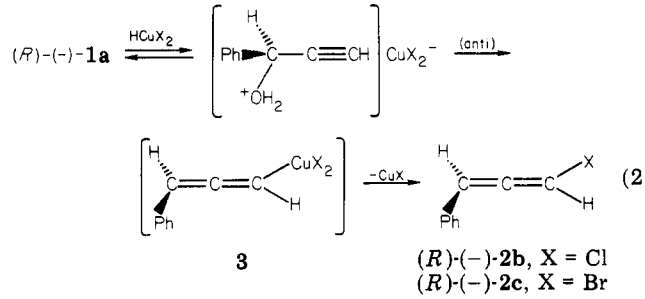
(1)

(*R*)-(–)-**1a** (*S*)-(+)-**2a**

([α]$^{20}_D$ (in EtOH) +90°), which corresponds to the *S* configuration (cf. ref 1); i.e., the formation of **2a** had occurred with syn stereoselectivity, albeit that (*S*)-**2a** was obtained in a very small enantiomeric excess (ee ≃ 6%).[6] The result appeared to be reproducible.

Quite remarkably, anti stereoselectivity was observed when **1a** was allowed to react with $HCuCl_2$ and $HCuBr_2$ (see also eq 2). Thus, treatment of optically pure (*R*)-(–)-**1a** with $HCuX_2$ (X = Cl or Br) during 5 min at 25 °C gave reproducibly and in high chemical yield (≥95%) the levorotatory allenes PhCH=C=CHX (**2b**, X = Cl, [α]$^{20}_D$ (in EtOH) –25°; **2c**, X = Br, [α]$^{20}_D$ (in EtOH) –280°). The negative value for [α]$_D$ in these cases corresponds with a preferent formation of the (*R*)-allenes (cf. ref 1). In the case of **2b** the optical yield is very low (ee ≃ 4%),[6,7] but for **2c** it is much better (ee ≃ 22%).[6] The stereoselectivity for the formation of (*R*)-**2b** from (*R*)-**1a** could be slightly improved (ee ≃ 8%) by using 0.5 equiv of $HCuCl_2$. When cuprates were used that had been prepared from CuX and excess of HX (cf ref 4), the enantiomeric purity of the allenes **2** decreased considerably. An excess of HX was therefore avoided during our experiments.[8]

Landor et al. reported that the amount of syn stereoselectivity in their case, viz., conversion of 3,4,4-trimethyl-1-pentyn-3-ol by $HCuBr_2$, was high.[4] The authors proposed a mechanism involving the rapid formation of a π-complex between the carbon–carbon triple bond of the alcohol and the cuprate $CuBr_2^-$ followed by a rate-determining S_Ni'-type reaction (cf ref 4). Such a mechanism could be valid for the reaction of **1a** with $HCuI_2$, but the low optical yield for this conversion indicates that other processes, e.g., formation of **2a** through the cation Ph^+-CHC≡CH leading to racemic **2a** and/or the occurrence of synchronous anti 1,3-substitution, must be important. It is even possible that the overall syn stereoselectivity is caused by a preferent occurrence of a reaction sequence involving two successive anti substitutions, viz., (i) conversion of (*R*)-**1a** into (*S*)-PhCH(I)C≡CH and (ii) conversion of this propargylic iodide into (*S*)-**2a**. We do not have evidence to exclude the latter route. The anti stereoselectivity for the $HCuCl_2$- and $HCuBr_2$-induced conversions of **1a** is similar to that reported in ref 1–3. Equation 2 presents a mechanistic proposal for these re-



(2)

3 (*R*)-(–)-**2b**, X = Cl; (*R*)-(–)-**2c**, X = Br

actions involving the initial protonation of the hydroxyl group of **1a** in order to improve its leaving group character, followed by the formation of the copper(III) intermediate **3**[9] in an anti 1,3-substitution reaction; reductive elimination

(1) Elsevier, C. J.; Meijer, J.; Tadema, G.; Stehouwer, P. M.; Bos, H. J. T.; Vermeer, P.; Runge, W. *J. Org. Chem.* **1982**, *47*, 2194.
(2) Elsevier, C. J.; Bos, H. J. T.; Vermeer, P.; Spek, A. L.; Kroon, J. *J. Org. Chem.* **1984**, *49*, 379.
(3) Muscio, O. J.; Jun, Y. M.; Philips, J. B. *Tetrahedron Lett.* **1978**, 2379.
(4) Landor, S. R.; Demetriou, B.; Evans, R. J.; Grzeskowiak, R.; Davey, P. *J. Chem. Soc., Perkin Trans. 2*, **1972**, 1995.
(5) Tadema, G.; Everhardus, R. H.; Westmijze, H.; Vermeer, P. *Tetrahedron Lett.* **1978**, 3935.
(6) The ee values are calculated assuming that the [α]$^{20}_D$ values that are given in ref 1 for the haloallenes **2** refer to optically pure compounds.
(7) The allene was contaminated with 5 mol % of PhCH(Cl)C≡CH.
(8) Alcohol **1a** can also be converted into allenes **2** by using only HX (water as solvent). For instance, reaction of **1a** with 2.0 equiv of HI (for concentration of HI, see under Materials) gave after 5 min a quantitative yield of allene **2a**; after shorter reaction periods, mixtures of **2a** and **1a** were obtained. When HCl or HBr instead of HI was used, the main product was initially the propargylic halide PhCH(X)C≡CH, which, under the conditions of the reaction, isomerized almost completely (≥98%) into the allenic halide PhCH=C=CHX (**2b**, X = Cl; **2c**, X = Br) by excess of HX. Such an initial formation of the propargylic halide has not been observed during the $HCuX_2$-promoted reactions of **1a**.

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