The Chromium Trioxide–3,5-Dimethylpyrazole Complex: a Mild and Selective Reagent for the Oxidation of Cyclopropyl Hydrocarbons

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The title complex selectively oxidises the methylene unit adjacent to a cyclopropane ring producing synthetically useful yields of the corresponding cyclopropyl ketones and/or products resulting from cleavage of the three-membered ring.

The chromium trioxide–3,5-dimethylpyrazole (3,5-DMP) complex, **1**, first introduced by Corey and Fleet[1] as a reagent for converting alcohols into carbonyl compounds, is now widely used for allylic and benzylic oxidation reactions.[2] In view of the extensive current interest in the selective functionalisation of saturated hydrocarbons,[3] we now report a hitherto unrecognised property of complex **1**, namely that it is a mild and selective oxidant of cyclopropyl hydrocarbons. Ring-

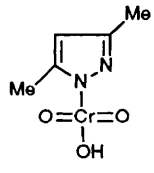

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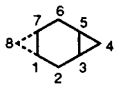
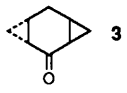
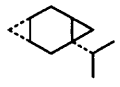
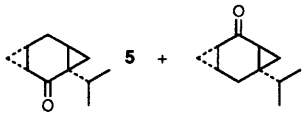
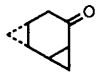
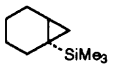
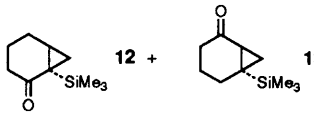
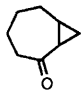
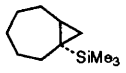
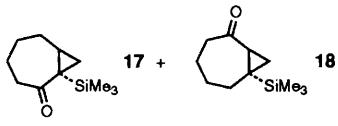
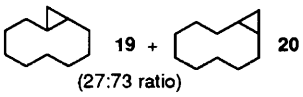
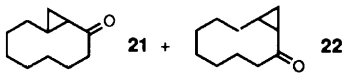
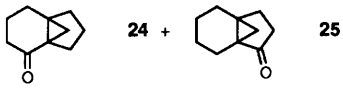
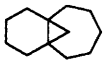
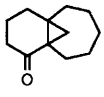
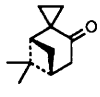
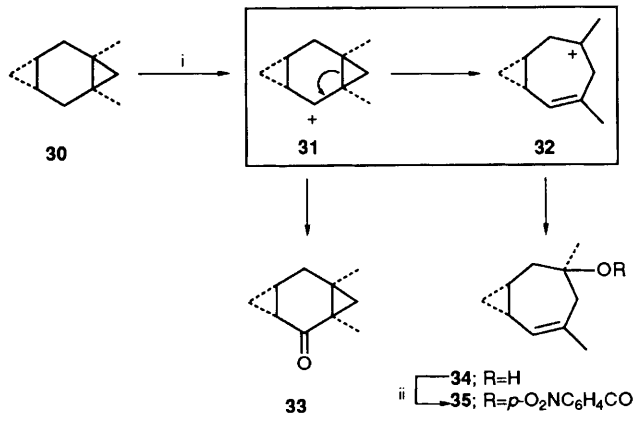
Table 1 Oxidation of ring-fused cyclopropyl hydrocarbons using complex **1**

Entry	Substrate(s)[a]	Conversion (%)	Product(s)	Yield[b] (%)	M.p. 2,4-DNPH[c] derivative(s)
1	 **2**	82	 **3**	98	216–218
2	 **4**	70	 **5** + **6**	8 (**5**)[d] 37 (**6**)[d]	192–193 (**6**)
3	 **7**	23	 **8**	62	137–139
4	 **9**	77	 **10**	35	162–163.5 (lit.[e] 158)
5	 **11**	59	 **12** + **13**	9 (**12**) 91 (**13**)[f]	137–153 (**12**)[g] 132–150 (**13**)[g]
6	 **14**	56	 **15**	8	190–191 (lit.[h] 188–189)
7	 **16**	12	 **17** + **18**	39 (**17**) 54 (**18**) (m.p. 56–57)	(**17**)[i] 128–130 (**18**)
8	 **19** + **20** (27:73 ratio)	30 (**19**) 96 (**20**)	 **21** + **22**	93 (**21**) 78 (**22**)	167–168 (**21**) 186–188 (**22**)
9	 **23**	62	 **24** + **25**	67 (**24**)[f] 3 (**25**)	179–180 (**24**)
10	 **26**	48	 **27**	82[f]	197–198
11	 **28**	75	 **29**	49	158–159

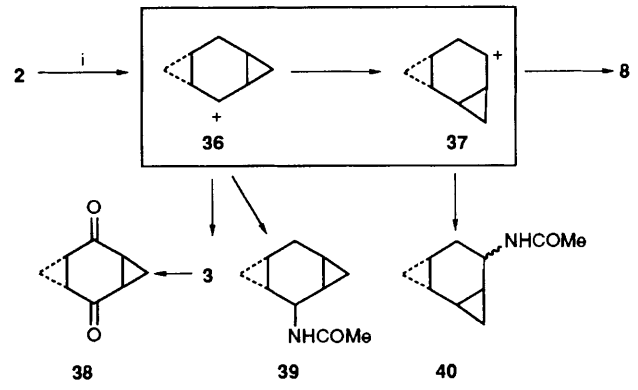
[a] Substrates were prepared by addition of dichlorocarbene to the appropriate cycloalkene or cycloalkadiene and subsequent reductive dechlorination of the resulting adduct under Bouveault–Blanc conditions. [b] As a percentage of substrate converted. [c] DNPH = dinitrophenylhydrazone. [d] The structures of the major and minor products obtained from the oxidation of **4** have been assigned on the basis that in the respective ^{13}C NMR spectra ketone **5** ($\delta_{C=O}$ 181.3) would exhibit a more pronounced γ-*gauche* effect than isomer **6** ($\delta_{C=O}$ 206.6). [e] G. Stork and J. Ficini, *J. Am. Chem. Soc.*, 1961, **83**, 4678. [f] Structure of this product confirmed by unequivocal synthesis. [g] These 2,4-DNPH derivatives were obtained as a mixture of geometric isomers. [h] A. Padwa and A. Battisti, *J. Am. Chem. Soc.*, 1972, **94**, 521. [i] The 2,4-DNPH derivative of compound **17** could not be formed because of competitive desilylation.

fused cyclopropanes, in particular, are smoothly converted into the corresponding cyclopropyl ketones.[4] Although two other reagent systems (ozone on silica[5] and RuO_4[6]) are reported to effect the same type of oxidation, the methodology described herein employs cheap and readily available reagents and involves the use of simple apparatus. Furthermore, these oxidation reactions, which are frequently very efficient, can be carried out on a preparative scale and useful levels of regioselectivity are often observed.

The results of treating a series of substrates with complex **1**, under conditions similar to those recommended[2a] for the allylic oxidation of alkenes (20 equiv. of **1**, dichloromethane as solvent, 3 h, −20 °C), are summarised in Table 1. The conversion of tricyclo[5.1.0.$0^{3,5}$]octane **2**[7] into the previously



Scheme 1 *Reagents and conditions*: i, CrO_3 (20 equiv.), 3,5-DMP (20 equiv.), CH_2Cl_2, −20 °C, 3 h; ii, *p*-$O_2NC_6H_4COCl$ (2 equiv.), pyridine, 25 °C, 48 h



Scheme 2 *Reagents and conditions*: i, CrO_3 (20 equiv.), CH_2Cl_2–MeCN (1 : 1), 0 °C, 3 h

uncharacterised tricyclo[5.1.0.0^{3,5}]octan-2-one **3**†‡ (entry 1) is representative in that a mixture of starting material and product(s) is always obtained but the conversions are generally high and, without exception, the components of the mixture can be readily separated by chromatography on silica. Extended reaction times did not provide enhanced yields of ketone **3**. Furthermore, under the same reaction conditions, chromium trioxide alone (*i.e.* no 3,5-DMP present) does not effect the conversion of **2** into **3**. Methylene units adjacent to a single ring-fused cyclopropyl group are oxidised by **1** (entries 3–10) and spiro-fusion of the same group also facilitates oxidation (entry 11). The reaction is sensitive to steric effects (entries 2, 5 and 7) since there is a strong preference for oxidation at the methylene unit remote from bulky ring-junction substituents. There also appears to be a significant preference for oxidation of methylene groups contained within six-membered rings. Thus, treatment of the [4.3.1]propellane **23** (entry 9) with complex **1** afforded a *ca.* 20 : 1 mixture of ketones **24** and **25**. Furthermore, oxidation of the [5.4.1]propellane **26** (entry 10) produced only ketone **27**; none of the isomeric compound, where the carbonyl group has been introduced into the seven-membered ring, could be detected.

Another noteworthy feature associated with the conversions detailed in Table 1 is that in no instance was evidence obtained for the formation of twofold oxidation products (*e.g.* diketones). Presumably, the electron-withdrawing effect of the first carbonyl unit, which can operate inductively through the cyclopropane ring(s), deactivates the remaining methylene towards oxidations. As further testimony to the sensitivity of the reaction towards electron-withdrawing groups, neither the 4,4,8,8-tetrachloro-[8] nor the 2-acetoxy-derivatives§ of **2** formed products on treatment with **1** [Weyerstahl and coworker[8] have reported that the former derivative of **2** can be converted into the corresponding ketone (19%) on treatment with chromium trioxide in acetic acid at 80 °C].

A number of experiments have cast some light on the mechanism of these oxidation reactions. For example, when the dimethyl derivative **30** (Scheme 1) of **2** was treated with **1**, under the standard conditions described above, ketone **33** (55% at 43% conversion, m.p. 2,4-DNPH derivative 209–210 °C) was the major product of reaction but significant quantities of the ring-cleaved product **34** (26% at 43% conversion) were also obtained. The structure of this latter product was confirmed by a single-crystal X-ray analysis of the derived *p*-nitrobenzoate **35** (m.p. 174–175 °C)¶ and the formation of both products can be rationalised by invoking early participation of the cyclopropylmethyl cation **31**. This intermediate could either be oxidised to the ketone **33** or undergo rearrangement to the homoallylic cation **32** which would then be oxidised to give the observed alcohol **34**. Some support for this mechanistic proposal stems from the observation that when lower concentrations of oxidant were employed increased quantities of compound **34** (relative to **33**) were obtained. Perhaps a more revealing experiment involved treating tricycle **2** (Scheme 2) with chromium trioxide (20 equiv.) at 0 °C in dichloromethane–acetonitrile (1 : 1) for 3 h. Under these conditions complete consumption of the starting material was observed and six products, compounds **3** (40%), **8** (16%), **38** (5%, m.p. 182–184 °C, lit.,[9] 186–187 °C), **39** (3%, m.p. 96–98 °C) and **40** (3% of a *ca.* 1 : 1 mixture of diastereoisomers), were obtained. All these products can be rationalised as arising from cation **36**. Thus, reaction of this cation with chromium oxide would deliver ketone **3** which is presumably the precursor to the diketone **38**. A Ritter reaction[10] involving **36** and the cosolvent acetonitrile would deliver, after aqueous work-up, the observed acetamido compound **39**. Alternately, a cyclopropylmethyl to cyclopropylmethyl cation rearrangement[11] of **36** would afford isomer **37** which could engage in an analogous series of reactions to give compounds **8** and **40**. In so far as this last reaction can be taken as a model for those involving complex **1**, the intermediacy of cyclopropylmethyl radicals in these oxidation processes seems unlikely (although the rapid oxidation of such a species to the corresponding cation cannot be discounted) since such intermediates would be expected to give products resulting from attack of the radical at the sp carbon (rather than nitrogen) of the acetonitrile.

We thank Professor A. L. J. Beckwith for valuable

† All new compounds had spectroscopic data (IR, NMR, mass spectrum) consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives. All new substances were obtained as racemates but only one enantiomer is depicted for the sake of clarity.

‡ Selected spectral data for **3**: ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ 0.66 (m, 2H), 1.17 (m, 2H), 1.29 (m, 2H), 1.47 (m, 2H) and 2.13 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C) δ 11.2 (d, C-5 and -7), 12.3 (dd, C-4 and -8), 20.2 (d, C-1 and -3), 20.9 (t, C-6) and 206.8 (s, C-2); IR, ν_{max}(NaCl, neat) 1688 cm^{-1}; *m/z* (EI, 70 eV) 122 (45%) [M] and 55 (100) [$C_4H_7^+$].

§ (1α,3β,5β,7α)-2-Acetoxytricyclo[5.1.0.0^{3,5}]octane was prepared in 60% yield from ketone **3** by a reduction ($NaBH_4$)–acetylation (acetic anhydride) sequence.

¶ *Crystal data* for **35**: $C_{17}H_{19}NO_4$, M = 301.3, monoclinic, space group $C2/c$, a = 33.439(4), b = 6.600(1), c = 14.205(3) Å, β = 96.76(2)°, U = 3113(2) Å^3, $F(000)$ = 1280, Z = 8, D_m = 1.282(5), D_c = 1.286 g cm^{-3}, μ = 7.15 cm^{-1} (Cu-Kα). Rigaku-AFC diffractometer (graphite-crystal monochromator, λ = 1.5418 Å), $2\theta_{max}$ = 100°, 1616 non-equivalent data measured at 292(1) K, isotropic refinement (SHELX-76[12]) with 631 data [$I > 2\sigma(I)$] converged at R = 0.083, R_w = 0.115 [$w = (\sigma^2|F_o| + 0.0003\,|F_c|^2)^{-1}$]. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, See Notice to Authors, Issue No. 1.

discussions and Dr David Kelly for the acquisition of NMR spectral data. We are grateful to the Australian Research Council for financial support.

Received, 22nd December 1992; Com. 2/06791I

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