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The Khand reaction of some trisubstituted alkenes. Uses of the catalytic version of the reaction

David C. Billington **, William J. Kerr, Peter L. Pauson
and (in part) Carlo F. Farnocchi

Department of Pure and Applied Chemistry, University of Strathclyde, Glasgow, G1 1XL (Great Britain)

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Abstract

Results are presented which suggest that in the absence of strong polar influences, 4,4,5-substituted cyclopentenones predominate over their 4,5,5-isomers when trisubstituted alkenes are employed in the Khand reaction. Double bond shifts prior to annellation are a feature of two of the examples studied. Efficient use of these relatively unreactive alkenes is made possible by employing an acetylene/carbon monoxide atmosphere to allow recycling of the cobalt carbonyl fragment.

Introduction

Increasing substitution of alkenes tends to diminish the yields of cyclopentenones from their reactions with alkynehexacarbonyldicobalt complexes (Khand reaction) [1]. Perhaps for this reason relatively few trisubstituted alkenes have been employed, although two examples. 2-ferrocenyl- and 2-phenylbicyclo[2.2.1]heptene, were included in one of our earliest reports on the reaction [2]. In these cases the 'additional' aromatic substituents appeared at the 5-position of the resulting cyclopentenone system. The preferred similar orientation of an aminoalkyl side-chain in recently reported examples is attributed to a specific coordinating effect of the amino groups [3]. In contrast, 1,2,3,3a,4,5-hexahydropentalene (**1a**) has been found to give the tricyclic ketone (**3a**) in which C(4) of the cyclopentenone system is the more highly substituted position [4] and the literature records at least one failure of a trisubstituted alkene to react [5]. There are also several examples of intramolecular reactions which involve successful use of trisubstituted alkenes, but in each of these cases the regiochemistry of the Khand reaction is predetermined by the structure of the enyne precursor [e.g. 6–9].

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* Present address: Merck Sharp and Dohme, Research Laboratories, Neuroscience Research Centre, Terlings Park, Eastwick Road, Harlow, Essex, CM20 2QR.

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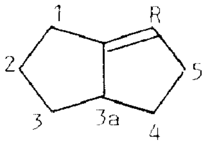
Discussion

We here report three examples studied during attempted natural product syntheses. The first of these required annelation of a cyclopentenone ring onto the double bond of 6-methyl-1,2,3,3a,4,6a-hexahydropentalene (**2b**). In their independent study, Serratosa's group [4] have noted that the lower homologue (**2a**) apparently undergoes rapid double bond shift under the reaction conditions so that only the product (**3a**) also obtainable from alkene (**1a**) could be isolated. We found that the trisubstituted alkene (**2b**) apparently underwent similar isomerisation to the tetrasubstituted alkene (**1b**) leading to a product mixture which contained the two ketones (**3b** and **4**) as the major components. A small amount of ketone derived from the unrearranged alkene (**2b**) was present, but it was not separated and its formulation as the cyclopentenone (**5**) must be regarded as tentative. To the best of our knowledge the formation of ketones (**3b**) and (**4**) is the only recorded example of the successful isolation of cyclopentenones from the Khand reaction of a tetrasubstituted alkene. That the high regioselectivity shown [4] by the trisubstituted alkene (**1a**) is lost on introduction of the additional substituent is hardly surprising.

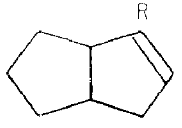
We had used 1-methylcyclopentene (**6**) in model experiments to try to find the optimum conditions for reactions of the bicyclic analogue (**2b**), and to determine the likely regioselectivity. The yields of "stoicheiometric" reactions were consistently much lower than for cyclopentene [10] even when a large excess of alkene was employed. Satisfactory yields based on the cobalt complex, ethynehexacarbonyldicobalt, were only obtained under "catalytic" conditions i.e. when free ethyne and carbon monoxide were also present. These are the conditions which were therefore chosen for the bicyclic alkene (**2b**). Although the present cases did not give yields in excess of 100% based on complex, it is known from earlier examples that true cobalt catalysis, in the sense that ethynehexacarbonyldicobalt is regenerated, is involved under these conditions. The first example was the catalytic reaction of norbornene [11] which gave a 75% yield based on alkene and 800% yield based on $Co_2(CO)_8$. A 150% yield based on ethynehexacarbonyldicobalt is recorded for its reaction with 2,5-dihydrofuran [12] and Magnus et al. [13] have confirmed that catalytic amounts of octacarbonyldicobalt suffice for intramolecular Khand reactions, although



1

(a) R=H

(b) $R=CH_3$



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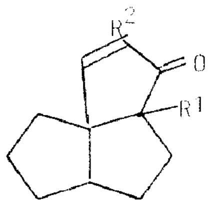
(a) R=H

(b) $R=CH_3$



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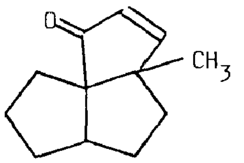
(a) $R^1=H$, $R^2=CH_2OSiMe_2Bu^t$

(b) $R^1=CH_3$; $R^2=H$



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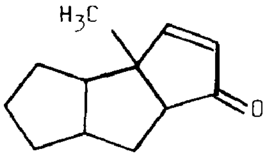

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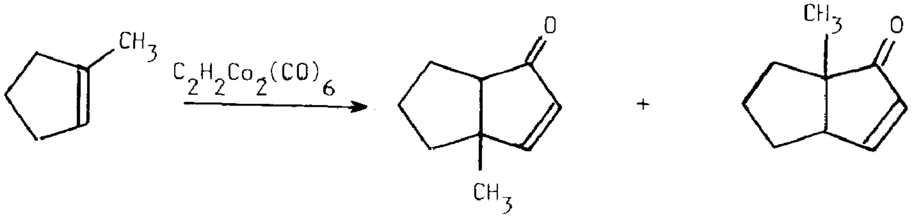


(6) (7) (8)

stoicheiometric quantities gave better yields. Yields based on cobalt complex obtained in the present work are summarised in Table 1.

The two possible regioisomers (**7** and **8**) are formed in the reaction of 1-methylcyclopentene (**6**) with ethynehexacarbonyldicobalt in approx. 9/1 ratio, i.e. with a moderately strong regioselectivity favouring the product with the methyl group at C(4) of the cyclopentenone system. The precise ratio proved to be somewhat variable (from 88/2 to 94/6) under different conditions, but the preferred direction is analogous to that reported for the bicyclic system (**1a**) [4].

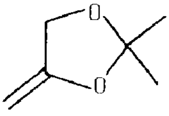
A third example showing similar regioselectivity to a high degree was found when we attempted the Khand reaction of ethynehexacarbonyldicobalt with the methylene-dioxolane (**9**). This gave none of the expected spirocyclic product, the only isolable cyclopentenone being the fused system (**10**) clearly derived from the endocyclic alkene (**11**). i.e. from another trisubstituted alkene. Whereas the isomerisation involved in this last case may be associated with considerably increased stability of the alkene formed, no comparable advantage is apparent in the isomerisations of the bicyclic alkenes (**2a**,**2b**). The methyl-substituted compound (**2b**) is the apparent sole product [14] of dehydration of the alcohol (**12**) and it is also formed by isomerisation of 1-methyleneperhydropentalene [15] suggesting that it is the

Table 1

Effect of an excess of alkene and presence of free alkyne on the yields of cyclopentenones from ethynehexacarbonyldicobalt (in benzene)

Alkene	Product(s)	Yields (%) stoicheiometric reaction	Excess alkene (×20)	Excess alkene $+CO/C_2H_2$
6	**7**+**8**	10	19	69
Cyclopentene	**13**	9	49	70
2b	**3b**+**4**(+**5**)	<1	6.5 [a]	24

[a] Without benzene in refluxing alkene (148° C) (15 equiv.).



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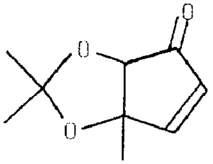

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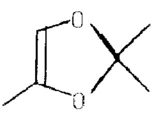

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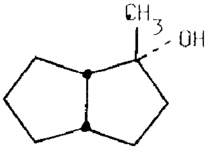

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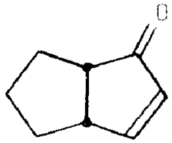

(13)

stable isomer. In a previous example of double bond migration prior to Khand reaction [16] the obviously favourable isomerisation of 4-methoxyallylbenzene to 4-methoxy-1-(1-propenyl)benzene represented only a minor pathway and allylbenzene itself reacted without similar rearrangement.

The perhydro-1-pentalenone required for the formation of the above alkene (**2b**) (via carbinol **12**) was obtained in the present work by two routes: The hydrogenation of the unsaturated ketone (**13**), itself formed from cyclopentene by Khand reaction and a slight modification of the published route from cyclooctene via epoxidation [17], isomerisation to octahydro-($1\alpha,3a\beta,6a\beta$)-1-pentalenol [18] and oxidation. Overall yields were similar (65–70%) but the second route was considered more convenient on a large scale. Details are given in the experimental section.

Experimental

Reactions of ethynehexacarbonyldicobalt were carried out under nitrogen. Evaporation was carried out under reduced pressure on a rotary evaporator. Alumina for column chromatography was Spence's grade UG1 100 mesh which had been neutralised by treatment with ethyl acetate, washed with ethanol then water and oven dried at 150 °C for 2 h. "Flash"-silica column chromatography was performed using MN-Kieselgel 60 (0.04–0.063 mm, 230–400 mesh) (Macherey–Nagel and Co) following the procedure of Still, Kahn and Mitra [19].

TLC was carried out using plastic sheets coated with 0.25 mm silica gel. Distillations of < 2 g quantities were carried out using a Büchi GKR-50 Kugelrohr apparatus at the oven temperatures and pressures quoted.

cis-4,5,6,6a-Tetrahydro-1-3aH-pentalenone (13). A mixture of cyclopentene (17 g, 250 mmol), ethynehexacarbonyldicobalt (17.1 g, 55 mmol) and benzene (350 cm^3) was heated under reflux for 2 days, cooled to 20 °C and filtered through Kieselguhr, the residue being washed with chloroform. The filtrate was evaporated and the residue chromatographed on an alumina column. Light petroleum (b.p. 40–60 °C) eluted residual organocobalt compounds and chloroform eluted the product which was further purified by "flash" chromatography or distillation (90–100 °C/15 torr) (Lit. [20]: b.p. 85–89 °C/14 torr), to give the ketone (**13**) (3.25 g, 49%), having IR and ^1H NMR spectra in agreement with lit. data [21] and giving a single peak on GLC (retention time 35.2 min on 5% FFAP at 80 °C).

This reaction was repeated using acetylene/carbon monoxide (1/1) in place of nitrogen atmosphere, cyclopentene (13.76 g, 200 mmol), the cobalt complex (3.12 g, 10 mmol) and benzene (100 cm^3) at 65 °C for 2 days ("catalytic" conditions) and the product isolated as above to give the ketone (**13**) (855 mg; 70% based on cobalt complex).

cis-Hexahydro-1-2H-pentalenone. (a) By hydrogenation of ketone (**13**): This ketone (3.25 g, 26.6 mmol) in methanol (100 cm^3) was stirred with 10% palladium-on-charcoal (100 mg) under one atmosphere of hydrogen until 595 cm^3 had been taken up. After removal of catalyst by filtration, the solution was evaporated, the residue redissolved in dichloromethane, dried ($MgSO_4$), and again evaporated to leave the product (3.19 g; 97%); IR and ^1H NMR spectra showed that hydrogenation was complete and were in good agreement with lit. data [22,23].

(b) From cyclooctene: Cyclooctene (220 g) was oxidised to its epoxide (106 g, 73% based on cyclooctene consumed; lit. [17]: 96%) by the method of Sheng [17]. Isomerisation [18] of the epoxide (63 g) yielded octahydro-($1\alpha,3a\beta,6a\beta$)-1-pentalenol (57.6 g, 92%; lit. [18] 80%). b.p. 84–86 °C/12 torr (Lit. [18]: 103–105 °C/25 torr) containing less than 1% cyclooct-2-en-1-ol (by ^1H NMR [17]).

A solution of this alcohol (2.52 g, 20 mmol) in acetone (100 cm^3) was cooled to 0 °C. Jones' reagent (prepared from chromium trioxide (7.0 g) and concentrated sulphuric acid (11.2 g) in water (30 cm^3)) was added slowly with stirring, keeping the temperature below 5 °C until the mixture had a persistent orange-brown colour. After a further 20 min stirring excess oxidant was destroyed by addition of saturated aqueous sodium sulphite solution and the acetone was removed in vacuo. The residue was extracted with chloroform (4×100 cm^3), the combined extracts were washed with water (100 cm^3), saturated sodium hydrogen carbonate solution (150 cm^3) and saturated sodium chloride (100 cm^3), and dried ($MgSO_4$). The solution was evaporated, and the ketone (2.34 g: 95%) isolated by distillation, b.p. 70–74 °C/15 torr; its spectra agreed with those of the sample prepared by method (a).

1,2,3,3a,4,6a-Hexahydro-6-methylpentalene (13b). Following a known method [14] *cis*-hexahydro-1-2*H*-pentalenone (4.96 g) was converted into the alkene (**2b**) (3.21 g; 66%; lit. [14]: 75%), b.p. 80–85 °C/60 torr (Lit.: b.p. [20] 153 °C/748 torr; b.p. [15] 57–59 °C/20 torr); the alkene gave a single peak on GLC (retention time 7.2 min on 5% Carbowax at 40 °C) and its IR, ^1H and ^{13}C NMR spectra supported homogeneity and were in agreement with published data [14,24,25]. Notably the ^1H NMR peak ($CDCl_3$) at δ 5.15 ppm (finely split t, 1H, H(5)) confirms structure (**2b**) by excluding the isomerised tetrasubstituted alkene (1b).

Reaction of 1,2,3,3a,4,6a-hexahydro-6-methylpentalene (2b) with ethynehexacarbonyldicobalt (1). Stoicheiometric reaction in refluxing benzene gave extremely low yields of ketonic product. Reaction was therefore effected under "catalytic" conditions: Ethynehexacarbonyldicobalt (624 mg, 2 mmol), the alkene (**2b**) (4.88 g, 40 mmol) and benzene (50 cm^3) were stirred under 1/1 ethyne/carbon monoxide at 65 °C for 10 days. Workup as in the preparation of ketone (**13**). Involving both alumina and "flash" silica gel chromatography, yielded a ketone mixture (85 mg, 24%) giving a single spot on TLC (R_f (ether) 0.51) and two main overlapping peaks (retention times 18 min and 19.2 min on a 5% FFAP at 125 °C) on GLC. ^{1}H NMR ($CDCl_3$, 250 MHz) showed a peak at a 2.70 ppm attributed to CH–C=O of isomer (**5**) along with peak doublets for its olefinic protons at δ 6.03 and 7.63 ppm. One of the isomers (**3b**) and (**4**) gave olefinic doublets at δ 6.08 and 7.44 ppm, the other at δ 5.98 and 7.32 ppm the total intensity of the olefinic protons peaks being in the correct ratio to the broad multiplet (δ 1.00–2.27 ppm) arising from the other 14 protons.

Reaction of 1-methylcyclopentene (6) with ethynehexacarbonyldicobalt. (a) Stoicheiometric reactions: 1-Methylcyclopentene (**6**) [26] (12.3 g, 0.15 mol) and the complex (9.36 g, 30 mmol) were heated under reflux in benzene (150 cm^3) until no more starting complex could be detected by TLC (3 h). After cooling, the mixture was filtered through Kieselguhr, the residue washed with chloroform and the combined filtrates evaporated under reduced pressure. The residue was chromatographed on neutral alumina and the ketonic fraction rechromatographed on 'flash' silica gel or distilled at 100–105 °C/15 torr. The product so obtained (761 mg, 19%) was a 9/1 mixture of 3*a*- (**7**) and 6*a*-methyl-4,5,6,6*a*-tetrahydro-1-3*aH*-pentalenone (**8**). The isomer ratio was determined by GLC using a 5% FFAP column at 60 °C. In agreement with literature data [27,28] the mixture showed NMR peaks for the major component [27] at δ ($CDCl_3$; 250 MHz) 1.33 (s, 3H, CH_3), 1.35–1.94 (m, 6H, H(4,5,6)), 2.26 (m, 1H, H(6a)), 6.08 (d, 1H, $J_{2,3}$ 5.57 Hz, H(2)) and 7.40 ppm (d, 1H, H(3)) and for the minor component [28] at δ 6.15 (dd, H(2)) and 7.49 (dd, H(3)). IR: $\nu_{max.}$ ($CHCl_3$) 2960, 2875, 1690, 1585, 1450, 1375, 1345, 1319, 1309, 1273, 1158, 1084, 1064, 982, 891, 835 cm^{-1}.

A somewhat different ratio (94/6) of ketone (**7**) to (**8**) was obtained (16% yield) with the reversed molar proportions (1/5) of alkene (**6**) to cobalt complex, whereas use of a 1/1 ratio merely lowered the yield. (b) Catalytic reaction: Reaction of the alkene (**6**) (3.28 g, 40 mmol) and the complex (624 mg, 2 mmol) in benzene (50 cm^3) was performed under an atmosphere of acetylene and carbon monoxide (1/1) at 65 °C for 3 days and the products isolated as above to yield a mixture of ketones (**7**) and (**8**). (188 mg, 69% based on cobalt complex: ratio 88/12).

5,7,7-Trimethyl-6,8-dioxabicyclo[3.3.0]oct-3-en-2-one (10). 4-Methylene-2,2-dimethyl-1,3-dioxolane (**9**) [29] (3.95 g, 34.6 mmol) was added dropwise to a solution of ethynehexacarbonyldicobalt (2.16 g, 6.9 mmol) in benzene (60 cm^3) and the solution then warmed to 65 °C for 6 h. The reaction mixture was cooled, filtered through celite and the solvent evaporated. The residual dark oil was chromatographed on neutral alumina to separate organometallic products from the slower-moving ketone, obtained as a red oil (310 mg). Further purification using a "flash" silica column, with ether/light petroleum (2/1) as eluant gave the ketone **10** as a colourless liquid (270 mg, 23%), δ ($CDCl_3$) 1.35 (3H, s, CH_3(7)), 1.45 (3H, s, CH_3(7)), 1.60 (3H, s, CH_3(5)), 4.70 (1H, s, H(1)), 6.10 (1H, d, $J_{3,4}$ 8 Hz, H(3)), 7.45 ppm (1H, d, H(4)): ν(CO) (liquid film) 1720 cm^{-1}. Found: C, 55.9; H, 6.3. $C_9H_{12}O_3$ calcd.: C, 56.2; H, 6.2%.

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References

1 (a) P.L. Pauson, Tetrahedron, 41 (1985) 5855; (b) P.L. Pauson in A. De Meijere and H. tom Dieck (Eds.), Organometallics in Organic Synthesis. Aspects of a Modern Interdisciplinary Field, Springer, Berlin, 1988.

2 I.U. Khand and P.L. Pauson, J. Chem. Soc. Perkin Trans., 1 (1976) 30.

3 M.E. Krafft, J. Am. Chem. Soc., 110 (1988) 968.

4 A.-M. Montana, A. Moyano, M.A. Pericas and F. Serratosa, Tetrahedron, 41 (1985) 5995.

5 B.E. La Belle, M.J. Knudsen, M.M. Olmstead, H. Hope, M.D. Yanuck and N.E. Schore, J. Org. Chem., 50 (1985) 5215.

6 M.J. Knudsen and N.E. Schore, J. Org. Chem., 49 (1984) 5025: N.E. Schore and M.J. Knudsen, ibid., 52 (1987) 569.

7 A.M. Montana, M.A. Pericas and F. Serratosa, personal communication.

8 V.A. Smit, A.S. Gybin, S.O. Veretenov and A.S. Shashkov, Izv. Akad. Nauk SSSR, Ser. Khim., (1987) 232 (Bull. Acad. Sci. USSR (1987) 211).

9 V.A. Smit, S.O. Simonyan, A.S. Shashkov, S.S. Mamyan, V.A. Tarasov and I.I. Ibragimov, Izv. Akad. Nauk SSSR, Ser. Khim, (1987) 234 (Bull. Acad. Sci. USSR, (1987) 213).

10 I.U. Khand and P.L. Pauson, J. Chem. Res., (1977) (S) 9; (M) 168.

11 I.U. Khand, G.R. Knox, P.L. Pauson, W.E. Watts and M.I. Foreman, J. Chem. Soc. Perkin Trans., 1 (1973) 977.

12 D.C. Billington, Tetrahedron Lett., 24 (1983) 2905.

13 P. Magnus, L.M. Principe and M.J. Slater, J. Org. Chem., 52 (1987) 1483.

14 J. Knotnerus and H. Schilling, Rec. Trav. Chim. Pays-Bas, 83 (1964) 414.

15 P.G. Gassman, J.J. Valcho, G.S. Proehl and C.F. Cooper, J. Am. Chem. Soc., 102 (1980) 6519.

16 I.U. Khand, E. Murphy and P.L. Pauson, J. Chem. Res., (1978) (S) 350, (M) 4434.

17 M.N. Sheng, Synthesis, (1972) 194.

18 J.K. Whitesell and P.D. White, Synthesis, (1975) 602.

19 W.C. Still, M. Kahn and A. Mitra, J. Org. Chem., 43 (1978) 2923.

20 W. Kirmse and L. Ruetz, Liebig's Ann. Chem., 726 (1969) 36.

21 T.K. Jones and S.E. Denmark, Helv. Chim. Acta, 66 (1983) 2377.

22 L.A. Paquette, O. Cox, M. Oku and R.P. Henzel, J. Am. Chem. Soc., 96 (1974) 4892.

23 J.D. Roberts and W.F. Gorham, J. Am. Chem. Soc., 74 (1952) 2278.

24 H.C. Brown and W.J. Hammar, Tetrahedron, 34 (1978) 3405.

25 J.K. Whitesell and R.S. Matthews, J. Org. Chem., 42 (1977) 3878.

26 A.C. Cope, C.L. Bumgardner and E.E. Schweizer, J. Am. Chem. Soc., 79 (1957) 4729.

27 J. Ficini and A. Maujean, Bull. Soc. Chim. France, (1972) 4392.

28 M. Karpf and A.S. Dreiding, Helv. Chim. Acta, 60 (1977) 3045.

29 H.O.L. Fischer, E. Baer and L. Feldmann, Ber., 63 (1930) 1732; H.D. Scharf and E. Wolters, ibid., 111 (1978) 639.