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THE KHAND REACTION

A CONVENIENT AND GENERAL ROUTE TO A WIDE RANGE OF CYCLOPENTENONE DERIVATIVES

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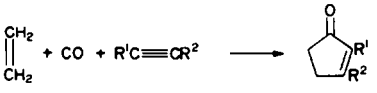
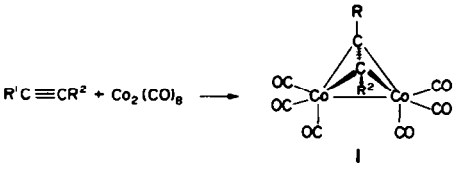
Abstract—The formation of cyclopentenones from alkynes, plus alkenes and cobalt carbonyl is reviewed, with special attention to the scope and the regio- and stereoselectivity of the reaction. Examples of experimental procedures are given and recent applications to the synthesis of biologically active natural products or analogues are described.

The Khand reaction[1] is the formation of cyclopentenones in a single step from an alkyne, via its hexacarbonyldicobalt complex, an alkene and carbon monoxide, present as a ligand in the complex. Thus in its simplest form, using ethylene as the alkene, the reaction can be formulated as:



(1)

More commonly the alkyne has been converted to its hexacarbonyldicobalt complex (Eq. 2) and the latter



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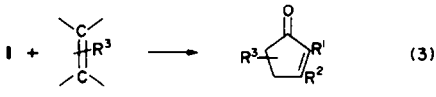
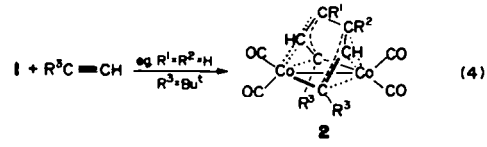
used in a stoichiometric reaction with the alkene (Eq. 3).[2]



(3)

The discovery of this reaction,[2,3] initially using strained alkenes, e.g. norbornadiene, arose from the postulate that these alkenes might insert into the alkyne complexes (1) in the same manner as alkynes were known to do. Two molecules of the latter add, forming the "flyover" complexes (2), as in reaction (4).[4] Further reaction or thermal or oxidative degradation of these complexes (2) leads to benzene derivatives (Eq. 5).



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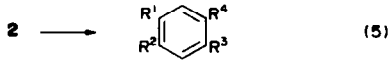

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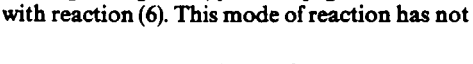
The complexes (2) appear to be the first isolable products in this system; no compound arising from the insertion of only one alkyne into complex (1) has been identified. By contrast, from reaction (3) which must involve alkene insertion, we have never been able to isolate intermediate complexes and we have found no product arising from the insertion of two alkene molecules. Thus the results of alkyne and alkene insertion reactions are substantially different. A further variation in behaviour is observed[5] in the reaction of alkenes bearing strongly electron withdrawing substituents and this appears to be the chief limitation of the cyclopentenone-forming reaction (3): Such alkenes (Y = CN, CO_2R, SO_2R, etc.) yield conjugated dienes in accord with reaction (6). This mode of reaction has not



(6)

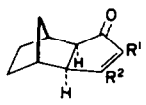
given sufficiently good yields to be attractive as a general synthetic route to such dienes, but it may prove useful in special cases. Mechanistically it seems probable that complex (1) initially inserts alkene to give a new complex which serves as a common intermediate, reacting either by insertion of a carbonyl ligand to yield a cyclopentenone (Khand reaction; Eq. (3)) or by hydrogen migration to yield a diene (Eq. 6). Styrene and substituted styrenes represent the borderline cases where both modes of reaction are observed.[6-8]

Early examples of these reactions have been reviewed by the present author and the late Dr I. U. Khand.[2] It is the purpose of the present article to emphasize the utility of the Khand reaction in organic synthesis and its simplicity. The valuable features of the reaction are therefore reviewed under the headings: (A) Specificity, (B) Scope and (C) Methods with a final section, (D), illustrating some typical uses.

(A) SPECIFICITY

The Khand reaction shows a high degree of both regio- and stereoselectivity. Already the initial experiments with norbornene derivatives[3c,9] showed that the products (3) had exclusively the *exo*-configuration and that terminal alkynes yielded at least predominantly the 2-substituted ketones (3, R^2 = H).

Thus, e.g. the propyne complex (**1**, R^1 = Me, R^2 = H)



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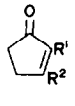

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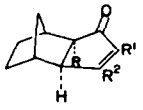
yields the 2-methylketone (**3**, R^1 = Me, R^2 = H). The further observation[9] that the complex of trimethylsilylpropyne (**1**, $R^1 = Me_3Si$, R^2 = Me) yields the 2-trimethylsilyl-3-methyl ketone (**3**, $R^1 = Me_3Si$, R^2 = Me) strongly suggests that the regioselectivity in respect of the alkyne moiety is determined by steric factors. Since acid hydrolysis of this product yielded the 3-methyl ketone (**3**, R^1 = H, R^2 = Me) the possibility of using a removable bulky group to change the overall regiochemistry is also established by this example.

The regioselectivity is high, but not complete. From reactions of the phenylacetylene complex (**1**, $R^1 = C_6H_5$, R^2 = H) (which we have used most widely for exploring the scope of the Khand reaction with respect to the alkene component) traces of isomeric products, presumably the 3-phenylcyclopent-2-en-1-one derivatives, have occasionally been isolated. Nevertheless, even relatively small differences in steric demand of the alkyne substituents can lead to substantial discrimination. Thus from the oct-2-yne complex (**1**, $R^1 = C_5H_{11}$, R^2 = Me) and ethylene, dihydrojasmone (**4**, $R^1 = C_5H_{11}$, R^2 = Me) and its regioisomer (**4**, R^1 = Me, $R^2 = C_5H_{11}$) are obtained in approximately 12.5:1 ratio and from reaction of *Z*-oct-5-en-2-yne as its complex (**1**, $R^1 = C_5H_9$, R^2 = Me) we isolated only jasmone (**4**, $R^1 = C_5H_9$, R^2 = Me).[6,10]

Regioselectivity with respect to the alkene component is much more variable and it is not yet clear what all the determining factors may be. 2-Aryl-(phenyl or ferrocenyl)-substituted bicyclo[2.2.1]hept-2-enes reacted with apparent regiospecificity[9] to give only the tricyclic ketones (**5**, R = Ph or Fc). Similarly only one regioisomer (**6**) was detected[11] as the ketonic product formed from the acetylene complex (**1**, $R^1 = R^2$ = H) with 2,2-dimethyl-2,5-dihydrofuran. The latter example suggests that steric factors are largely responsible leading to the product with the bulkier group adjacent to the ketonic function (whereas the previous example could have involved steric or electronic influences). On the assumption that the first C—C bond is formed between the alkene and alkyne moieties (i.e. before CO insertion) it is tempting to rationalize such results as involving bond formation between the less hindered ends of these components.



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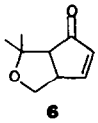

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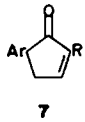

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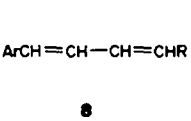

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But a number of results do not fit into this simplistic pattern. Thus whereas styrene and substituted styrenes give at least predominantly cyclopentenones (**7**) and dienes (**8**) in which the aryl groups are at the end of the four-carbon chain[6-8] in reaction with, e.g. the phenylacetylene complex (**1**, R^1 = Ph, R^2 = H), 1-n-alkenes yield[9] approximately 1:1 mixtures of the 4- and 5-alkyl-2-phenylcyclopent-2-en-1-ones (**9** and **10**; e.g. R = Me or C_6H_{13}).

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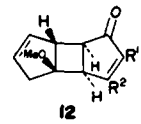

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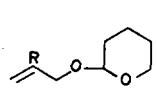
Apparently high regioselectivity, not immediately relatable to the above examples was observed[12] in the reactions of 1-methoxybicyclo[3.2.0]hepta-3,6-diene (**11**) to give the tricyclic products (**12**). The most surprising results however are those obtained with allyl and 2-methylallyl 2-tetrahydropyranyl ether (**13**). Since the immediate vicinity of the double bond does not differ greatly from that in a terminal n-alkene it was unexpected that the allyl ether (**13**, R = H) reacted with the but-2-yne complex (**1**, $R^1 = R^2$ = Me) to give[13]



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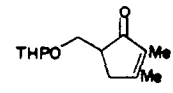

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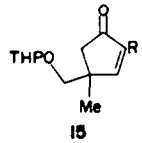

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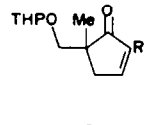

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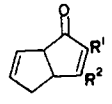
exclusively the ketone (**14**). More remarkably the methyl derivative (**13**, R = Me) not only gives a mixture of 4,4- (**15**) and 5,5-substituted compounds (**16**) in which the former predominates, but with both the acetylene (**1**, $R^1 = R^2$ = H) and propyne complexes (**1**, R^1 = Me, R^2 = H) it was shown that the ratio of these products **15**:**16** (R = H or Me) increases with increasing reaction temperature.[14]

Cyclopentadiene and 6,6-disubstituted fulvenes undergo Khand reaction apparently regiospecifically, the alkyne moiety being attached to the 1-position of the five-membered ring to yield[15] the 4,6-dihydro-1(3a)pentalenones (**17** and **18**). The divergent behaviour of other conjugated dienes is described in the following section.



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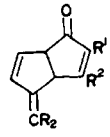

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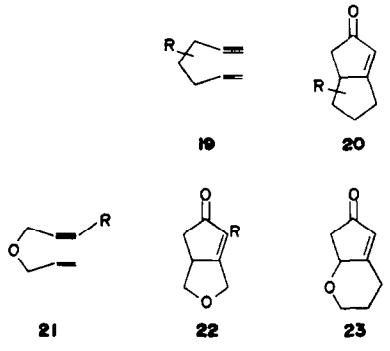
A high degree of stereoselectivity is evident in the apparently exclusive formation of the tricyclo[5.2.1.$0^{2,6}$]decenones (**3** and **5**) and the tricyclo[5.3.$0^{1,7}$.$0^{2,6}$]decenones (**12**) mentioned above and of related systems. Whether acyclic alkenes also react stereoselectively is not known. Preliminary experiments[10] with *cis* and *trans* isomers of both 1,2-dideuterioethylene and but-2-yne gave mixtures of *cis* and *trans* products, but this may have resulted from enolisation during workup.

(B) SCOPE

(1) *The metal complex.* As yet no serious effort has been made to determine whether other types of alkyne–metal complexes can replace the hexacarbonyl–dicobalt system in the Khand reaction. Minor modification of the cobalt complexes by replacement of one or two carbonyl ligands by phosphines has been tried to a limited extent in our laboratory.[10] These experiments suggest that addition of tri-n-butylphosphine oxide is advantageous in selected cases; the phosphines examined reduced both the reaction rate and the product yield although the reaction occurred in most cases. Since a complex of an unsymmetrical alkyne becomes chiral when one CO group is replaced by another ligand the possibility of achieving asymmetric induction with phosphine-substituted complexes deserves study.

(2) *The alkyne.* All simple (unsubstituted, alkyl or aryl substituted) alkynes work well in the Khand reaction although the product yields from diphenylacetylene were, in the few cases tried, significantly lower than those from less heavily substituted alkynes. Polar groups remote from the triple bond appear to have little effect, but those in close proximity are commonly detrimental. Thus ethoxyacetylene gives the complex (1, R^1 = OEt; R^2 = H) in poor yield (30%) and this rather unstable compound gave only a few percent of a ketone, $C_{12}H_{16}O_2$, presumably (3, R^1 = OEt, R^2 = H), when allowed to react with norbornene.[16] The stable complexes of propargyl alcohol and of methyl propiolate failed to yield ketonic products when treated with the same alkene,[16] but phenylthioacetylene has given moderate yields of several 2-phenylthiocyclopentenones.[17]



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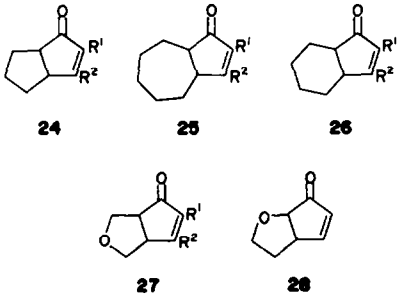
Complexes of 3- and 4-en-1-ynes have been used in Khand reactions as has hepta-2,5-diyne complexed on one triple bond. Thus free double or triple bonds conjugated with or one atom removed from the complexed triple bond do not interfere. Earlier results to this effect[18] have recently been confirmed in syntheses of jasmone and jasmonic acid.[10] Complexes of 5-en-1-ynes have not been tried in similar reactions but may be expected to behave similarly since hex-1-en-5-yne has been shown[19] not to undergo an intramolecular Khand reaction. Such intramolecular reaction, i.e. cyclization, becomes possible when the multiple bonds are more widely separated. This was first demonstrated by Croudace and Schore[19] and exploited in an efficient synthesis of coriolin by Exon and Magnus.[20] Yields of tetrahydropentalenones (**20**) were found to depend greatly on the substituents in the octenyne precursors (**19**). Allyl propargyl ethers (**21**) cyclize similarly[21] to 3a,4,5,6 - tetrahydro - 5 - oxa - 2(3H)pentalenones [7 - oxabicyclo(3.3.0)oct - 1 - en - 3 - ones] (**22**) and the ketone (**23**) appears to have been formed (though not obtained pure)[19] from pent-4-ynyl vinyl ether.

(3) *The alkene.* With the exception, already mentioned, of alkenes bearing strongly electron-withdrawing groups, most simple alkenes seem to be suitable substrates for the Khand reaction. Strained alkenes including norbornene[3c,9] and cyclobutene derivatives[12] and related compounds[2] react under somewhat milder conditions but good results have been obtained with ethylene and with many simple alkenes.[6] For acyclic alkenes there is some indication that increasing substitution at the double bond lowers reactivity. Among cycloalkenes, cyclopentene and cycloheptene reacted efficiently to give, respectively, tetrahydro-1(3aH)pentalenones (**24**) and hexahydro-1(3aH)azulenones (**25**) whereas cyclohexene only reacted sluggishly to give poor yields of hexahydro-1-indenones (**26**).[6]



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Like cyclopentene, 2,5-dihydrofurans react readily to give the corresponding products **27** or **6** in good yield.[11] 2,3-Dihydrofuran reacts similarly[22] yielding 6-oxa - 4,5,6,6a - tetrahydro - 1(3aH)pentalenones (**28**) and, whereas early attempts[23] with some other vinyl ethers and esters were unsuccessful, both vinyl t-butyl ether and vinyl acetate are reported (without details)[19] to give mixtures of 4- and 5-t-butoxy-, viz. acetoxy-cyclopentenones. The only vinylthio ether tried, phenyl vinyl sulfide proved too easily polymerizable.[17]

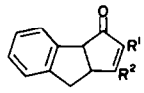
The effect of electron withdrawing groups in leading to the alternative reaction (Eq. (6)) and the "intermediate" position of styrene derivatives which yield both cyclopentenones (**7**) and dienes (**8**) has been referred to in the introduction. The results[7,8] for some substituted dienes are collected in Table 1; they reveal no consistent pattern. In particular no consistent enhancement of diene yield results from attachment of either the electron-withdrawing *p*-halo or the more electron-withdrawing tricarbonylchromium group (this group has frequently been compared to a *p*-nitro substituent in its effect). Moreover both 2-vinylfuran and vinylferrocene, which must be regarded as electron-rich styrene analogues yielded dienes, accompanied by at most traces of ketonic products. On the other hand indene, 1,2-dihydronaphthalene and acenaphthylene, which may all be regarded as cyclized derivatives of styrene, gave predominantly ketonic products, opening a convenient route to the tri- and tetracyclic cyclopentenone derivatives (**29–31**).

Diolefins have given widely varying results with no apparent pattern. Only one allene, cyclonona-1,2-

Table 1. Effect of substitution of styrene on the yields of cyclopentenones (7) and dienes (8) (R = Ph) on reaction with phenylacetylenehexacarbonyldicobalt (1, R^1 = Ph, R^2 = H)[7,8]

Styrene p-X—$C_6H_4CH{=}CH_2$	Products from free styrenes: % ketone (7) (Ar = p-XC_6H_4)	Products from free styrenes: % diene (8) (Ar = p-XC_6H_4)	Products from chromium complexes $(OC)_3Cr(p\text{-}XC_6H_4CH{=}CH_2)$: % ketone (7) Ar = $(OC)_3Cr(p\text{-}XC_6H_4)$	Products from chromium complexes $(OC)_3Cr(p\text{-}XC_6H_4CH{=}CH_2)$: % diene (8) Ar = $(OC)_3Cr(p\text{-}XC_6H_4)$
X = H	12	39	37	32
X = Me	13	26	39	29
X = MeO	27	42	38	35
X = F	35	—	29	44
X = Cl	8	8	—	29

diene has been tried;[24] it reacts readily, but the structure of the product, probably **32**, has not been firmly established. Cyclopentadiene and fulvenes react like mono-olefins giving regioselectively the products (**17**, **18**) mentioned above.[15] Cyclohexa-1,3-diene gave a series of products[25] which were clearly cyclopentenone derivatives, but had incorporated two alkyne moieties from the cobalt complexes (1, R^2 = H). Their



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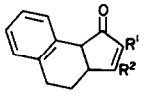

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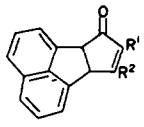

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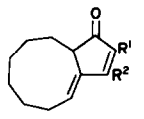

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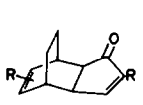

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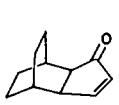

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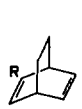

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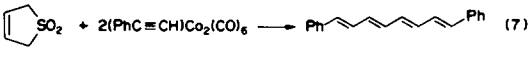
structures **33** were established by showing that the unsubstituted product **33** (R = H) and the Khand reaction product **34** from bicyclo[2.2.2]oct-2-ene could be hydrogenated to the same saturated ketone, tricyclo[5.2.2.$0^{2,6}$]undecan-3-one. The first step must be a cobalt-complex catalyzed Diels–Alder addition of the alkyne moiety from the complex (**1**) to cyclohexa-1,3-diene yielding the bicyclo[2.2.2]octa-2,5-dienes (**35**) whose less substituted double bond then reacts further. The intermediates (**35**) could not be isolated suggesting that the second step is appreciably faster than the first.[25] In contrast to the behaviour of cyclopenta- and -hexadienes, no product could be obtained from cyclohepta-1,3-diene and buta-1,3-diene (preferably as its sulfur dioxide adduct, 2,5-dihydrothiophene dioxide) reacted with the phenylacetylene complex (1, R^1 = Ph, R^2 = H) to give[2] in very low yield all-*trans*-1,8-diphenyloctatetraene as the only isolated product (Eq. (7)); butadiene is thus reacting at both termini in the manner of alkenes with electron withdrawing groups [cf. Eq. (6) and the formation of dienes (**8**) from styrene derivatives].



(7)

(C) METHODS

As a laboratory method the Khand reaction is a very simple process. Octacarbonyldicobalt is available commercially and can be stored in a tightly stoppered vessel in a refrigerator for long periods. It reacts with alkynes at room temp (or with gentle warming if more rapid reaction is desired) in ether, alkanes or other unreactive solvents and most alkynes give high yields of stable complexes (**1**). The reaction proceeds with liberation of CO and should therefore always be conducted in a good hood. All metal carbonyls must be assumed to be toxic, but the volatility of the complexes (**1**) like that of the precursor, $Co_2(CO)_8$, is sufficiently low so that their toxicity presents no handling problem. The complexes of simple alkynes (up to at least eight carbons) are stable to distillation in a good vacuum. They are only weakly adsorbed on alumina and on a small scale or for complexes of more complex alkynes column chromatography is the most convenient method of purification. The following two are typical preparations while the third is that of a complex of unusually low stability which is formed in rather low yield.

(*But-2-yne*)*hexacarbonyldicobalt* (1, $R^1 = R^2 = CH_3$).[13] A soln of octacarbonyldicobalt (12 g, 35 mmol) in light petroleum (b.p. 40–60°) (100 ml) under nitrogen is stirred and maintained at 10–15° while but-2-yne (2.8 ml, 1.9 g, 35 mmol) in the same solvent (50 ml) is added during 0.5 hr. The mixture is then stirred for a further 5 hr. The red soln is filtered through celite, then concentrated under reduced pressure and chromatographed on neutral alumina, using the same solvent to elute the product (11.3 g, 94%). (But-2-yne)hexacarbonyldicobalt is a dark red oil which solidifies on refrigeration.

(*Methyl non-8-ynoate*)*hexacarbonyldicobalt* [1, $R^1 = (CH_2)_6CO_2Me$; R^2 = H].[26] Methyl non-8-ynoate (6.0 g, 36 mmol) was added in one portion to a stirred soln of octacarbonyldicobalt (13.3 g, 39 mmol) in light petroleum (b.p. 60–80°) (50 ml) under N_2. Stirring at room temp was continued until the evolution of CO appeared to cease and then for a further 2 hr to ensure complete reaction. Workup as in the preceding experiment yielded the complex (16.0 g, 91%) as a dark red oil, ν_{CO} (as liquid film): 2090, 2050, 2020, 1740 cm^{-1}; (in cyclohexane solution): 2051, 2027, 2018, 1728 cm^{-1}; δ ($CDCl_3$) 6.05 (1H, s, HC≡), 3.70 (3H, s, OCH_3), 2.90 (2H, t, $CH_2C{\equiv}$), 2.36 (2H, t, CH_2CO) and 1.6 ppm (8H, m, CH_2).

(*Ethoxyacetylene*)*hexacarbonyldicobalt* [1, R^1 = OEt, R^2 = H].[27] To a stirred soln of octacarbonyldicobalt (10 g, 29.2 mmol) in light petroleum (b.p. 40–60°) (300 ml) under N_2, ethoxyacetylene[28] (2 g, 28.5 mmol) in the same solvent (25 ml) was added dropwise over 0.5 hr and stirring was then continued at room temp for 3 hr. Workup as in the preceding experiments gave the complex (3 g, 29.5%) as a relatively unstable red oil, δ($CDCl_3$) 5.20 (1H, s, HC≡), 3.80 (2H, q, CH_2) and 2.40 ppm (3H, t, CH_3).

Typical properties of other simple alkyne complexes (**1**) are: Acetylene complex (1, $R^1 = R^2$ = H):[29] m.p. 13.0–13.6°; b.p. 64–66°/3.5–4 Torr. Diphenylacetylene complex (1, $R^1 = R^2$ = Ph):[29] m.p. 109.5–110° (purple crystals from MeOH); sublimes at 90°/1 Torr.

Propargyl alcohol complex (**1**, $R^1 = CH_2OH$, $R^2 = H$):[29] m.p. 52.2–52.6° (orange–red needles from light petroleum).

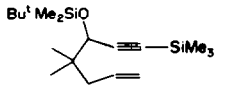
Reactions of alkyne complexes (**1**) with simple alkenes generally proceed at convenient rates at 80–120° and with the more reactive (strained) alkenes at 60–70°. However, little effort has been devoted to optimizing conditions (temp, choice of solvent) in individual cases. If the "catalytic" version of the reaction (Eq. (1)) is to to be used, a large excess of alkene will generally be required to minimize further reaction of the complex (**1**) with alkyne (Eqs (4) and (5)). Where the need for such excess is not an obvious disadvantage it is not necessarily preferable to isolate the complex before treating it with alkene (Eq. (3)), although this has been the common practice. The one-step process (Eq. (1)) is particularly appropriate for intramolecular Khand reactions, but even here isolation of the intermediate complex is possible since the cyclization step requires higher temp.

The beneficial effect of tributylphosphine oxide-substitution referred to in Section B can be achieved by simple addition of the phosphine oxide to the reaction mixture [i.e. it is not necessary to isolate the substituted analogues of the Co complexes (**1**)]. An example of this method is included below although it is not yet known how generally the yields of Khand reactions can be enhanced in this way.

Examples

Khand reactions by the single step procedure from the free alkyne:

3a,4,5,6,7,7a - *Hexahydro* - 4,7 - *methanoinden* - 1 - *one* (**3**, $R^1 = R^2 = H$).[3c] A soln containing octacarbonyldicobalt (1 g, 3 mmol) and bicyclo[2.2.1]hept-2-ene (norbornene) (3 g, 32 mmol) in iso-octane (100 ml) was stirred, first under acetylene, and then under 1:1 acetylene–CO at 60–70° until gas absorption ceased (total *ca* 1550 ml). The mixture was concentrated and the residue chromatographed on neutral alumina. Light petroleum b.p. (40–60°)–benzene (1:1) eluted acetylenehexacarbonyldicobalt (~70 mg). Benzene–$CHCl_3$ (1:1) then eluted a yellow oil which was distilled to yield **3** ($R^1 = R^2 = H$) (3.54 g, 74%), b.p. 101–102°/15 Torr, which formed colourless crystals from pentane, m.p. 32°, ν_{CO} 1695 cm^{-1}.



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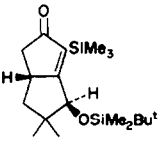


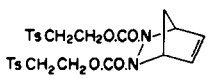
37

The bicyclo[3.3.0]*octenone* (**37**).[20] The enyne (**36**) was heated with 1.0 equiv of octacarbonyldicobalt in CO-saturated heptane at 110° in a sealed tube to give **37**, b.p. 128°/0.5 Torr in 79% yield together with 3% of its 8-epimer.

Reactions via isolated complexes (**1**). 1 - (2 - *Tetrahydropyranyloxyethyl*) - 3a,4,5,6 - *tetrahydro* - 5 - *oxa* - 2(3H)*pentalenone* (**22**, R = CH_2CH_2OTHP).[21] Allyl 5 - (tetrahydropyranyloxy)pent - 2 - yn - 1 - yl ether (10 g, 4.46 mmol) and octacarbonyldicobalt (15.39 g, 4.5 mmol) were stirred in light petroleum (b.p. 40–60°) (300 ml) under N_2 at room temp for 2 hr. (CO evolution appears to be complete well within that period.) Chromatographic purification on neutral alumina, eluting with ether–light petroleum (1:3), yielded as the major fraction the complex (**1**, $R^1 = CH_2CH_2OTHP$, $R^2 = CH_2OCH_2CH{=}CH_2$) (19.44 g, 85%).

This complex (19.44 g, 3.8 mmol) dissolved in iso-octane (250 ml) was stirred under CO and warmed to 60° for 24 hr (doubling this time did not increase the yield). The mixture was filtered through Kieselguhr, the filtrate evaporated using a rotary evaporator, and the residue chromatographed on neutralized alumina. Light petroleum eluted some unchanged complex and $CHCl_3$ then eluted the product. This was further purified by "flash" chromatography on silica gel using 30% EtOAc in ether as solvent. The ketone **22** (R = CH_2CH_2OTHP) (3.93 g, 41%) was isolated as an oil which was pure as judged by TLC and by ^1H and ^{13}C-NMR spectroscopy.

2 - *Methyl* - 4,6a - *dihydro* - 1(3aH)*pentalenone* (**17**, R^1 = Me, $R^2 = H$).[15] Propynehexacarbonyldicobalt (5.0 g, 15 mmol) and cyclopentadiene (4.0 g, 60 mmol) were heated under reflux in toluene (100 ml) with magnetic stirring for 5 hr under N_2. During this time the colour of the mixture changed from deep red to brown. The filtered soln was evaporated using a rotary evaporator and the residue was redissolved in benzene–light petroleum and chromatographed on neutral alumina. Light petroleum was used to elute unreacted Co complex and benzene–$CHCl_3$ (9:1) eluted **17** (R^1 = Me, $R^2 = H$) which was further purified by distillation at 100° (bath temp)/0.1 Torr; yield: 1.15 g (55%).



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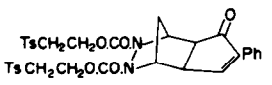


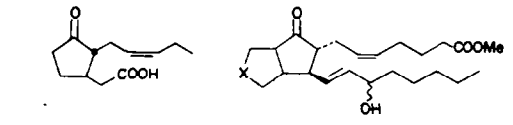
39

The ketone (**39**).[30] A soln of complex **1** (R^1 = Ph, $R^2 = H$) (5.3 g, 13.6 mmol) and **38** (6.7 g, 12.2 mmol) in toluene (300 ml) was stirred at 65–70° under N_2 for 6.5 hr. After being left at room temp overnight the mixture was filtered through Kiesulguhr and the filtrate was evaporated under reduced pressure. The solid residue was powdered and washed repeatedly with light petroleum and then dissolved in toluene and chromatographed on silica gel. Toluene–EtOAc (1:1) eluted unreacted **1** (R^1 = Ph, $R^2 = H$) (160 mg) and MeOH then eluted **39** (5.4 g, 65%) which separated as a fawn powder, m.p. 117–120° on cooling its concentrated MeOH soln to −70°.

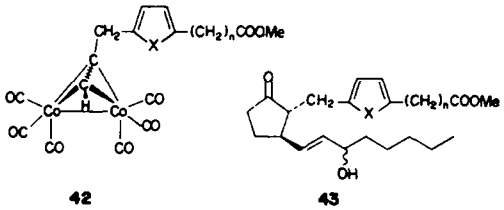
2 - *Pentyl* - 4,5,6,6a - *tetrahydro* - 5 - *oxa* - 1(3aH) - *pentalenone* (**27**, $R^1 = C_5H_{11}$, $R^2 = H$).[10] The hept-1-yne complex (**1**, $R^1 = C_5H_{11}$, $R^2 = H$) (5.0 g, 13 mmol), tri-n-butylphosphine oxide (2.6 g, 12.9 mmol) and 2,5-dihydrofuran (9.0 g, 130 mmol) were dissolved in hexane (200 ml) and heated to reflux under N_2 for 48 hr. The mixture was filtered, the filtrate evaporated under reduced pressure and the residue chromatographed on neutral alumina. Light petroleum eluted cobalt complexes, and 1:1 $CHCl_3$–light petroleum then eluted **27** ($R^1 = C_5H_{11}$, $R^2 = H$) (1.75 g, 69%) as a pale yellow oil; this distilled at 110° (oven temp)/0.2. Torr as an almost colourless oil. Under similar conditions in the absence of tributylphosphine oxide yields of 35–40% were obtained.

(D) USES

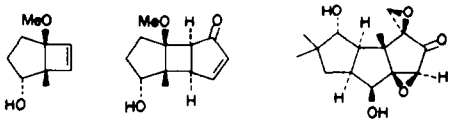
The Khand reaction is finding increasing use in the synthesis of a wide variety of natural products and of analogues desired for biological testing. Among the simplest naturally occurring cyclopentenones it has led to improved routes to jasmone (**4**, R^1 = (*Z*)—$CH_2CH{=}CHC_2H_5$, R^2 = Me), a valuable perfume constituent and jasmonic acid (**40**), a plant growth regulator and to various analogues.[10] The range of simple cyclopentanoid antibiotics which have become more accessible by this method include methylenomycins A[11] and B[13] and sarkomycin.[11] Syntheses of prostaglandin analogues, e.g. compounds (**41**, X = CH_2 or O) could be effected via ketones **24** or **27** (R^1 = (*Z*)-$CH_2CH{=}CH{-}(CH_2)_3CO_2Me$, R^2 = H) obtainable by Khand reactions of (*Z*)-methyl non-5-en-8-ynoate.[17,26] Making use of Nicholas' observation[31] that the propargyl alcohol complex (**1**, $R^1 = CH_2OH$, $R^2 = H$) is readily converted to the stable and electrophilic cationic complex (**1**, $R^1 = CH_2^+$, $R^2 = H$) allowed the facile syntheses of the complexes (**42**, X = O, $n = 2$ or X = S, $n = 1$) which were similarly elaborated[1] to prostaglandin analogues (**43**).



40 41



42 43



44 45 46

Schore and Sampath[32] have given a brief description of the regio- and stereoselective conversion of the bicyclo[3.2.0]heptene derivative (**44**) by Khand reaction with acetylene to the tricyclic ketone (**45**); the latter after activation of the OH group as tosylate underwent ring-opening to a hydroazulenoid dione suitable for the elaboration of hydroazulenic terpenes and as mentioned earlier, Exon and Magnus[20] made the bicyclic ketone (**37**) as an intermediate in a synthesis of coriolin (**46**).

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