Vinyl esters as ethylene equivalents in the Khand annulation reaction

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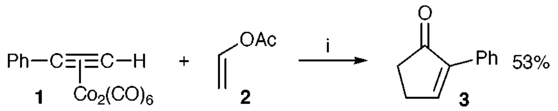
A preparatively convenient and mild method for modified Khand cycloadditions is described; vinyl esters are employed as the olefinic reaction partner to provide cyclopentenone products more normally obtained with ethylene.

The simple one step cobalt carbonyl mediated annulation of an alkyne, an alkene, and carbon monoxide to form substituted cyclopentenones (the Khand reaction)[1] has emerged as one of the most widely used organometal-based transformations in organic synthesis. Indeed, in recent years the development of modified techniques for promoting this reaction has led to its increased utilisation in a wide variety of synthetic endeavours.[1,2] In particular, the application of amine *N*-oxide promoters has allowed the annulations to be performed under mild reaction conditions to deliver highly improved product yields.[3] More specifically, studies in our own laboratory have led to *N*-oxide techniques which allow the application to both asymmetric cyclisation strategies[4] and to the establishment of markedly improved procedures for use with gaseous alkenes such as ethylene.[2h,5] Here we report the discovery of a novel use of non-gaseous ethylene equivalents in the Khand cyclisation.

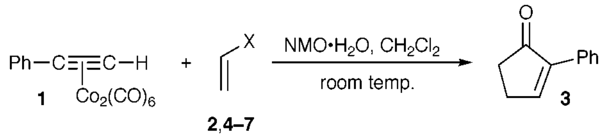
With a view to gaining access to (poly)oxygenated cyclopentenones and, more especially, with the advent of the mild amine *N*-oxide strategies, we envisaged that it would be possible to employ relatively sensitive vinyl esters as olefinic substrates. Since the phenylethyne–cobalt complex **1** was known[6,7] to give mixtures of 4- and 5-ethoxy-1-phenylcyclopent-2-en-1-one in poor yield when treated with ethyl vinyl ether under the generally less effective traditional reaction conditions, this complex was utilised in our initial experiments with vinyl acetate **2**. To our surprise, under the *N*-oxide conditions shown in Scheme 1 the only organic product isolated was the monosubstituted 2-phenylcyclopent-2-en-1-one **3**, lacking the anticipated acetate functional unit. Despite the moderate 53% yield, we recognised that this result had considerable potential as the basis for the development of a procedure which would employ what could be considered as a non-gaseous ethylene equivalent in Khand cycloadditions. To this end, we sought to optimise this modified Khand process by varying the reaction promoter, the vinyl ester, and the general reaction conditions.

In the reaction shown in Scheme 1, the ketone **3** had been obtained using trimethylamine *N*-oxide dihydrate at 45 °C. On the other hand, by employing the alternative mild oxidant, *N*-methylmorpholine *N*-oxide monohydrate ($NMO\cdot H_2O$),[3a] we found that the same class of transformation could be promoted at room temperature. In turn, this *N*-oxide was adopted for use in comparative experiments. As can be seen from Table 1, in reactions with complex **1**, a range of vinyl esters (**2**, **4**–**6**) all successfully afforded the cyclopentenone **3**. Additionally, use of vinyl bromide **7** also led to the formation of the same enone product.†



Scheme 1 *Reagents and conditions*: i, $Me_3N^+–O^-\cdot 2H_2O$ (9 equiv.), toluene–MeOH (10:1), 45 °C.

Table 1 Modified Khand reactions of vinyl substrates with phenylethyne complex **1**[a]



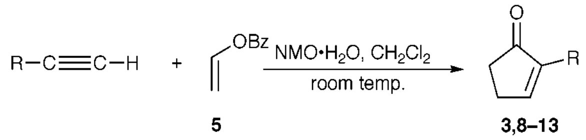
	X	Yield of **3** (%)
2	AcO	52
4	CF_3CO_2	50
5	BzO	58
6	Bu^tCO_2	31
7	Br	54

[a] 9–10 equiv. of $NMO\cdot H_2O$ employed.

Based on the results shown in Table 1, vinyl benzoate **5** was selected for further optimisation. Subsequently, it was established that slow (syringe pump) addition of the *N*-oxide promoter ($NMO\cdot H_2O$) over a 3 h period led to an excellent 80% yield of **3** at room temperature.‡ Indeed, the enhanced efficiency of this modified Khand process now compares favourably with the optimum yields achieved when using ethylene gas with $Me_3N^+–O^-\cdot 2H_2O$ and complex **1**; ethylene reaction at 40 °C and 25–30 atm provides a 71% yield of **3** whilst reaction at room temperature and 1 atm proceeds in 55% yield.[2h,5b]

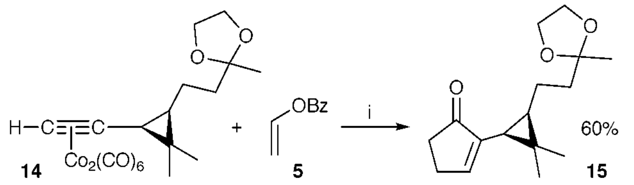
Having developed the slow addition procedure, these conditions were applied to a range of alkyne complexes (Table 2).§ Overall, we have found that the efficiency of the new vinyl benzoate technique is at least comparable with the optimum ethylene methods and, in most instances (where a comparison can be made), significant enhancement in the yield of cyclopentenone can be realised. A particularly vivid example of the improved efficacy of the ethylene equivalent method is provided when THP-protected propargyl alcohol is utilised as the alkyne substrate; using vinyl benzoate with $NMO\cdot H_2O$ at

Table 2 Modified Khand reactions of vinyl benzoate **5** with alkynes[a]



R	Product	Yield (%)
Ph	**3**	80
n-C_5H_{11}	**8**	77
Me_3SiCH_2	**9**	45
$THPOCH_2$	**10**	87
$THPO(CH_2)_2$	**11**	80
$HO(CH_2)_2$	**12**	61
$HOCH_2$	**13**	33

[a] Typically the alkyne $Co_2(CO)_6$ complex and excess vinyl benzoate (as co-solvent)¶ are stirred as $NMO\cdot H_2O$ (8–10 equiv.) is added over 0.5–3 h as a solution in CH_2Cl_2 before stirring is continued at room temp.



Scheme 2 *Reagents and conditions*: i, NMO·$2H_2O$ (10 equiv.), CH_2Cl_2, 2 h addition, room temp.

room temperature an excellent 87% yield of cyclopentenone **10** is achieved, whereas the maximum yield obtained under the optimum ethylene conditions was only 33%.[2h,5b]‖

As a final example, and to show the utility of the modified methods in natural product synthesis, we chose to employ alkyne complex **14**. In our previously reported total synthesis of (+)-taylorione,[2h,5a] the key step in our sequence towards this target had been the Khand reaction of **14** with ethylene. When reacted with vinyl benzoate under the conditions described here (Scheme 2), complex **14** gave cyclopentenone **15** in a 60% yield.** This result constitutes an improvement in the carefully optimised yield of 41% obtained for the same transformation with ethylene under ambient conditions. On the other hand, it is not equal to the best autoclave yield of 81% achieved with $Me_3N^+–O^-\cdot 2H_2O$ at 40 °C and 25 atm. Nonetheless, it is worth noting that, in the instances where higher yields are achievable using gaseous alkenes, autoclave facilities and conditions of elevated temperature and pressure are required. In contrast, the ethylene equivalent procedures disclosed here show how cheap, readily available and easily handled vinyl esters can be employed under ambient conditions to provide cyclopentenone products in yields which are at least competitive with and, more usually, improved over those of the equivalent optimised ethylene process.

In the developed modified Khand process it is clear that the isolated cyclopentenones are the products of reduction. In this respect, the C–O cleavage and subsequent replacement of the ester oxygen with H must involve a low oxidation state cobalt species, as this would be expected, under the reaction conditions, to be the only available reducing agent. Additionally, the reaction only proceeds to give the reduced products under inert (N_2) atmospheres. However, when using vinyl acetate **2** with complex **1** in air only a very low yield (7%) of the 5-acetoxycyclopentenone is obtained. We believe that the required hydrogen atom to complete the reduction process is supplied from water (*e.g.* from the hydrated *N*-oxide). This theory was supported when the reaction of **1** and **2**, promoted by anhydrous NMO, was performed in the presence of excess D_2O and exclusively yielded 5-deuterio-2-phenylcyclopent-2-en-1-one. Such regioselective incorporation of deuterium also implies that the reductive cleavage occurs after the coupling of the alkyne and alkene.

In summary, we have developed a novel method by which vinyl esters can be utilised as non-gaseous ethylene equivalents in the Khand annulation. The mild conditions and simple techniques employed provide significant advantages, both in terms of practical convenience and, in the majority of cases explored, reaction yield, over the corresponding gaseous alkene procedures.

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Notes and references

† Under more traditional conditions of elevated temperature with no *N*-oxide promoters, in reaction with complex **1**, vinyl bromide had been shown to give the product of reductive debromination, cyclopentenone **3**, in the low yield of 19% (ref. 8).

‡ Performing the NMO slow addition experiments for the reaction of complex **1** with vinyl benzoate **5** at a range of higher or lower temperatures (from −70 to 40 °C) led to less efficient cyclisations and lower yields of **3**.

§ All compounds exhibited satisfactory analytical and spectral data.

¶ Excess vinyl benzoate is readily recoverable on completion of the reaction.

‖ Using thermal conditions with no promoter, THP-protected propargyl alcohol completely failed to yield any cyclopentenone products when reacted with ethylene (ref. 9).

** This result provides the ketal protected form of the recently reported (+)-nortaylorione (ref. 10) and constitutes a formal total synthesis of this natural product, which has been prepared from **15** by our novel PPh_3/CBr_4 ketal deprotection method [ref. 2(*h*), 5(*a*), 11].

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