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Nitrous Oxide-Promoted Pauson-Khand Cycloadditions

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Abstract

A Pauson-Khand cycloaddition of alkynes, alkenes, and carbon monoxide, promoted by cobalt carbonyl and nitrous oxide to furnish cyclopentenones is described. Preliminary mechanistic experiments suggest that nitrous oxide functions in a similar manner to the *N*-oxide promoters typically employed in Pauson-Khand reactions. Only dinitrogen and carbon dioxide are produced as a consequence of the activation mechanism, thus avoiding high molecular weight reagents and the build up of basic byproducts. The chemistry is done using equimolar amounts of alkyne, alkene, and dicobalt octacarbonyl, and is performed directly from the acetylenic component without having to presynthesize a cobalt-alkyne complex. Terminal acetylenes were suitable substrates, as was solid calcium carbide, and the corresponding adducts were isolated in good yields. Furthermore, two sequential [4+3] and [2+2+1] cycloadditions were performed, generating functionalized cyclopentenones in only two steps from readily available starting materials.

Graphical Abstract

The Pauson-Khand reaction (PKR) is a [2+2+1] cycloaddition between an alkyne, an alkene, and carbon monoxide to yield cyclopentenones.¹ It was first discovered in the early 1970s as a stoichiometric reaction between acetylenedicobalt-octacarbonyl **1a** (R=H) and norbornene **2a** at elevated temperatures to yield the cycloadduct in moderate yield.²

The accepted mechanism (Scheme 1, A)³ was proposed based on observed regiochemistry of **3a**, and has been largely supported by DFT calculations⁴ and mass spectrometry.⁵ After formation of the dicobalt acetylene complex **1**, dissociation of a molecule of CO from **1** to form **4** must occur so that an alkene can coordinate to generate **5**, which goes on to form the cyclopentenone product **3**. The most common method for formation of **4** is the application

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ASSOCIATED CONTENT

Supporting Information

Experimental details; ¹H, ¹³C NMR, HRMS, and EA of new compounds.

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of a promoter, typically amine *N*-oxides.⁶ The amine *N*-oxide is required to be used in 5–10 fold excess to get synthetically useful yields of the cyclopentenone adducts,⁷ generating substantial amount of waste. Thus, it is somewhat surprising that the simplest *N*-oxide, nitrous oxide (N₂O), has never been used as a promoter in this reaction. Replacing the commonly employed trimethylamine *N*-oxide (TMAO) with N₂O reduce the amount of waste generated. Moreover, nitrous oxide is inexpensive and widely available, yet there are few applications of the gas as a reagent in chemical synthesis.⁸ Most transition metal catalysed or mediated processes that currently utilize N₂O involve direct transfer of the oxygen atom of N₂O to the transition metal center.⁹ However, we hypothesized that if N₂O could oxidize the CO ligand rather than cobalt,¹⁰ we could promote the PKR, and avoid the need for large excesses of solid oxide promoters (Scheme 1, B).

We began the study by comparing the isolated yields of cyclopentenone **3b** when the cycloaddition was performed in the presence of 1 equivalent of Co₂(CO)₈ and either 1 equivalent of a solid *N*-oxide promoters or in the presence of N₂O at 40 °C in acetonitrile (Table 1). We found that at that loading TMAO was an effective promoter of the PKR (entry 1), but *N*-methylmorpholine *N*-oxide (NMO) required higher loading in accordance with previously reported studies⁷ (entries 2 vs 3) to be effective. Nicotinamide *N*-oxide (NNO) was ineffective, and **3b** was produced in low yields among other unidentifiable materials (entry 4). We were pleased to note that performing the PKR in an N₂O-saturated acetonitrile solution gave cyclopentenone **3b** in 80% yield after 20 hours (entry 5). Extending the reaction time to 24 h improved the isolated yield of **3b** to 86% (entry 6). Performing the reaction at room temperature led to a slight reduction in isolated yield of **3b** (entry 7); performing the reaction in the total absence of promoter led to only trace **3b** (entry 8). We attempted to further improve the yield of the cycloadduct by varying the solvent (entries 8–12), but the reaction performed best in MeCN.

To determine whether N₂O was in fact acting in an analogous manner to other *N*-oxides, we compared in situ FTIR data for the reaction between the phenylacetylene-cobalt hexacarbonyl complex **1b** and both TMAO and N₂O. The generation of CO₂ was observed at 2338 cm⁻¹ upon addition of each promoter, though rapid outgassing of the solution prevented kinetic analysis of the two processes (Figure 1). While production of CO₂ is consistent with the oxidative extrusion of a CO ligand from the hexacarbonyl intermediate **1b** and formation of the putative pentacarbonyl species **4b**, we cannot rule out a more complex role for N₂O at this time.

We then turned to examining the scope of the alkyne component in the reaction (Table 2, top). To synthesis the parent cyclopentenone, we opted to use the solid reagent calcium carbide (**6a**) rather than gaseous acetylene to avoid concurrent introduction of two gaseous reagents. Calcium carbide, though exceedingly inexpensive, is not often employed as an acetylene surrogate.¹¹ We were pleased to note that CaC₂ was an effective substrate when used with 2 equivalents of water, and the cyclopentenone **3a** was isolated in good yield.¹² Phenylacetylene **6b** was an excellent substrate, yielding cyclopentenone **3b** in high yield. Electronically different, whether electron-rich (**6c**) or electron-poor (**6d** and **6e**) were somewhat less effective, and products **3c–3e** were isolated in somewhat lower yields. The internal alkyne dimethyl acetylenedicarboxylate **6f** was an excellent substrate, and the

product **6f** was isolated in good yield. Other functional groups were well-tolerated, and cyclopentenones containing coordinative alcohol and nitrile functional groups, **3h** and **3i** were isolated in good yields. Norbornadiene was also an effective partner in the PKR,¹³ and adducts **3j-3l** were isolated in generally good yield.

The intermolecular PKR is typically limited to olefins with either a low LUMO or those that possess a pendant Lewis base for secondary coordination to cobalt, but otherwise contain little functionality.^{7,14} We were interested in applying more functionalized alkenes to the PKR. The [3.2.1] and [3.2.2] bicyclic olefins **8a-8c** were particularly interesting as they are easily constructed from cyclic butadienes and ureas via [4+3] cycloadditions,¹⁵ and contain many synthetic handles for downstream transformations. We thus subjected bridged bicyclic alkenes **8a-8c** to our standard conditions. Though not as strained as the [2.2.1] bicyclic alkenes,¹⁶ these olefins were ready participants in the PKR, and densely functionalized cyclopentenones **3m-3o** were produced in good yields (Table 2, bottom). All cyclopentenones were isolated as single isomers, and *exo*-selectivity was determined by comparing acquired spectral data to known compounds **3a-b**, **3f-h**, **3j-l** and extrapolating that to unknown compounds **3c-e**, **3i**, **3m-o**.

Finally, we demonstrated the applicability of these reaction conditions to the cyclization of a 1,6-enyne (eq 1). The malonate derivative **9** smoothly reacted with CO₂(CO)₈ in the presence of N₂O to give the [5,5] bicyclic compound **10** in high yields (89%).

In conclusion, N_2O has been used for the first time as a promoter in the Pauson-Khand reaction. Its usage avoids the build-up of basic waste in situ that other often used promoters (NMO, TMAO) leave behind. We have preliminary evidence that N_2O oxidatively removes a CO ligand from the cobalt complex, but more detailed mechanistic explorations are warranted. We found that N_2O promoted the cycloaddition between alkynes and bridged bicyclic olefins in moderate to good yields, and could be executed directly from the alkyne with no need to presynthesize the cobalt alkyne complex. Our application of sequential [4+3] and [2+2+1] cycloadditions combines inexpensive and readily available starting materials to complex, densely functionalized tricyclic ring systems in only two steps.

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Figure 1.

In situ FTIR data comparing the activation of the cobalt-phenylacetylene complex **1b** (top) as promoted by TMAO (middle) and N₂O (bottom). The x-axis shows the region of CO₂ absorbance, and the z-axis begins at the addition of the *N*-oxide.

A: Typical intramolecular PKP and truncated mechanism (ref. 18) **B: Our approach**

- no pre-synthesis of acetylene complex **1** required
- only gaseous byproduct

Scheme 1.

Summary of cobalt-mediated Pauson-Khand cycloadditions.

Table 1.Selected optimization experiments in the N₂O mediated PKR.^a

Entry	R ₃ NO	Solvent (M)	T (°C)	T (h)	Yield% (3a) ^a
1	TMAO	MeCN	40	20	69
2	NMO	MeCN	40	20	29
3	NMO ^b	MeCN	40	20	75
4	NNO	MeCN	40	24	Intractable Mixture
5	N ₂ O	MeCN	40	20	80
⇒ 6	N₂O	MeCN	40	24	86
7	N ₂ O	MeCN	20	24	64
8	-	MeCN	40	24	Trace
9	N ₂ O	Toluene	40	24	74
10	N ₂ O	DMF	40	24	10
11	N ₂ O	THF	40	24	77
12	N ₂ O	DCM	40	24	40
13	N ₂ O	CHCl ₃	40	24	52

^aYields are of material isolated by silica gel chromatography.^b6 eqs. Of NMO.

See supporting information for further details.

Table 2.

Scope of the intermolecular PKR between alkynes **1a-1i** and norbornene **2a** as promoted by nitrous oxide.^a