Construction of tetracyclic ring systems by $Co_2(CO)_8$-catalyzed tandem [2 + 2 + 1]/[2 + 2 + 2] cycloaddition reaction of diynes: a simple one-pot reaction†

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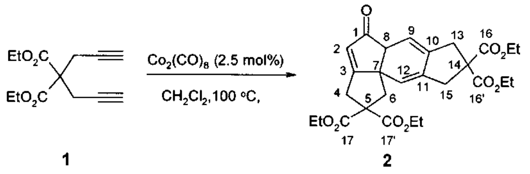
The $Co_2(CO)_8$-catalyzed tandem [2 + 2 + 1]/[2 + 2 + 2] cycloaddition reaction of terminal diynes under CO produces an unnatural novel tetracyclic compound.

Transition metal-catalyzed cycloaddition reactions of unsaturated substrates have provided many prominent methods for the construction of complex cyclic compounds.[1] Among them, the [2 + 2 + 1] cycloaddition provides a powerful tool for the assembly of five-membered ring containing polycyclic natural products. In particular, the Pauson–Khand [2 + 2 + 1] cycloaddition has attracted much attention for the preparation of a variety of cyclopentenone systems.[2] However, cyclopentadienones[3] have played no role in five-membered ring construction due to their high reactivity in Diels–Alder reactions, even though some cyclopentadienone derivatives are known. Transition metal-mediated [2 + 2 + 1] cycloaddition of two alkynes with CO can be a good way to generate and stabilize cyclopentadienones. However, the application of this method to organic synthesis has been hampered[4] by low yields, and the requirement for the presence of specific substituents, and the necessity of a demetalation step, even though $Fe(CO)_5$ or $CpCo(CO)_2$ have successfully been employed in some intramolecular carbonylative cycloaddition reactions.[5,6] All the reported reactions are stoichiometric. In the studying the Pauson–Khand reaction,[7] we became interested in the cycloaddition reaction of hepta-1,6-diynes employing $Co_2(CO)_8$ as catalyst because no successful examples of catalytic [2 + 2 + 1] cycloaddition reactions of α,ω-diynes had been reported.

Here we report a facile construction of unnatural novel tetracyclic compounds by the $Co_2(CO)_8$-catalyzed tandem [2 + 2 + 1]/[2 + 2 + 2] cycloaddition reactions of diynes under CO.

Reaction of diethyl dipropargylmalonate **1** in CH_2Cl_2 in the presence of 2.5 mol% $Co_2(CO)_8$ at 100 °C for 2 days under 20 atm of CO gave a tandem [2 + 2 + 1]/[2 + 2 + 2] cycloaddition reaction to produce the tetracyclic enone derivative **2** in 85% yield as the sole product (Scheme 1 and Table 1).†

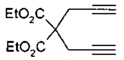
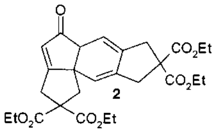
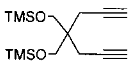
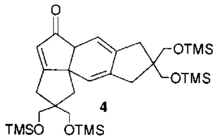
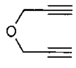
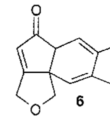
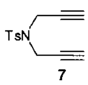
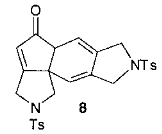
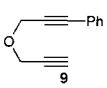
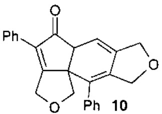
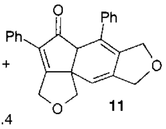
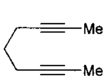
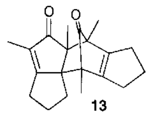
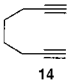
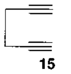
The structure of **2** was established by ^1H and ^{13}C NMR spectroscopic investigations (COSY, long range COSY, DEPT, HETCOR, long range HETCOR, phase sensitive NOESY, and 2D-INADEQUATE),‡ mass spectrometry and elemental analysis. No isomerized products were observed. The reaction involves the formation of four carbon–carbon bonds. Although this multibond formation reaction seems to be complex, it is simple and provides a unique pathway to a tetracyclic framework. The reaction of a 4,4-*gem*-disubstituted 1,6-diyne **3**, under the same reaction conditions, gave a tetracyclic enone derivative **4** in 78% yield. The present reaction can be extended to the use of an oxygen-containing ether. Subjecting the oxygen-containing substrate **5** to the same reaction conditions provided the oxatetracyclic enone derivative **6** in 35% yield. The nitrogen containing substrate **7** produced azatetracyclic enone derivative **8** in 89% yield. All the terminal diynes except dipropargyl ether gave high yields. For the mono-substituted



1 **2**

Scheme 1

Table 1 Cycloaddition reactions of diynes [a]

Diyne	Cycloadduct	Yield (%)[b]
 **1**	 **2**	85%
 **3**	 **4**	78%
 **5**	 **6**	35%
 **7**	 **8**	89%
 **9**	 **10** +  **11** 10 : 2.4	80%
 **12**	 **13**	19%
 **14**	—	NR
 **15**	—	NR

[a] $Co_2(CO)_8$ (2.5 mol%) CO (20 atm), 100 °C, CH_2Cl_2. [b] Isolated yields.

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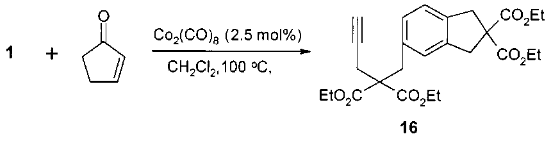
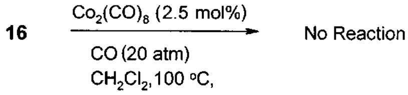
† Synthetic and spectroscopic details for **2**, **4**, **6**, **8**, **10** and **13** are available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/2099/

1,6-diyne **9**, a 10 : 2.4 mixture of two regioisomers (**10** and **11**) was obtained in 80% yield. For the disubstituted 1,6-diyne **12**, a [4 + 2] cycloaddition between [2 + 2 + 1] cycloadducts gave **13** in 19% yield with concomitant formation of unidentified polymeric materials. The steric effect of substituents at the external terminus of the diyne substrates is an important factor for the second [2 + 2 + 2] cycloaddition to proceed. Substrates (**14** and **15**) bearing substituents at the external termini of the alkyne and substrates having tethers lengthened or shortened by one carbon did not afford the corresponding tetracyclic compounds.

The following observations may provide some clues to help understand the catalytic reaction. Treatment of **1** with $Co_2(CO)_8$ in the presence of cyclopentenone afforded **16**[8] (Scheme 2). Cyclopentenone was not involved in the cycloaddition reaction. Resubjecting **16** to the original cyclization conditions ($Co_2(CO)_8$, CH_2Cl_2, 20 atm CO, 100 °C, 2 days) gave no corresponding cycloaddition product (Scheme 3).



Scheme 2



Scheme 3

Thus, the [2 + 2 + 2] cycloaddition reaction between diyne substrates does not occur before the [2 + 2 + 1] cycloaddition between CO and a substrate. We presume that initially a [2 + 2 + 1] cycloaddition between diyne and carbon monoxide catalyzed by $Co_2(CO)_8$ gives the corresponding bicyclic cyclopentadienone, and a subsequent [2 + 2 + 2] cycloaddition reaction between the bicyclic cyclopentadienone and diyne catalyzed by $Co_2(CO)_8$ leads to the tetracyclic cyclopentenone. We cannot rule out the possibility of alkene insertion to give a cobaltacycloheptadiene intermediate and reductive elimination of the tetracyclic cyclopentenone.

In summary, the reaction described herein demonstrates a novel one-step entry to unprecedented tetracyclic enone systems from acyclic starting substrates. The starting materials are readily prepared, and the resulting fused tetracycles have an unnatural framework which is difficult to prepare using conventional methods.

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Notes and references

‡ *Selected data* for **2**: δ_H($CDCl_3$) 5.94 (d, *J* 2.2, H^2), 5.78 (dddd, *J* 5.6, 2.2, 2.0, 1.9, H^9), 5.34 (ddd, *J* 2.3, 2.0, 1.9, H^{12}), 4.23 (q, *J* 7.0, CH_2CH_3, 2H), 4.15–4.08 (m, CH_2CH_3, 6H), 3.56 (dd, *J* 17.2, 2.2, H^4), 3.17 (d, *J* 17.2, H^4), 3.04 (ddd, *J* 5.6, 2.2, 2.0, H^8), 3.01 (ddd, *J* 16.7, 2.0, 2.0, H^{13}), 2.87 (ddd, *J* 16.7, 2.2, 2.2, H^{13}), 2.85 (dd, *J* 16.6, 2.0, H^{15}), 2.82 (dd, *J* 16.6, 2.3, H^{15}), 2.55 (d, *J* 14.1, H^6), 2.15 (d, *J* 16.6, H^6), 1.23 (t, *J* 7.0, CH_3, 3H), 1.19 (t, *J* 7.1, CH_3, 3 H), 1.18 (t, *J* 7.0, CH_3, 3H), 1.15 (t, *J* 7.1, CH_3, 3H); δ_C($CDCl_3$) 210.05, 186.07, 171.40, 170.90, 170.85, 170.71, 135.78, 134.33, 125.56, 119.30, 115.76, 62.12, 62.04, 61.47, 61.42, 59.12, 58.56, 56.39, 54.81, 47.06, 38.51, 38.20, 34.64, 13.83, 13.79, 13.78, 13.78, ν_{max}(Et_2O)/cm^{-1} 1737.2, 1718.0 (CO) [HRMS: calc. 500.2046 (M^+), obs. 500.2043].

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