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# New Substituted Cyclopentenones by Coupling of Pauson-Khand and Michael-type Reactions

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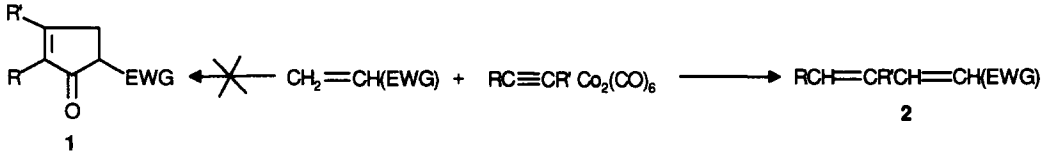
**Abstract.** A new catalytic synthesis of substituted cyclopentenones from alkynes, alkenes bearing an electron-withdrawing group and CO in the presence of $Co_2(CO)_8$ is reported. It consists of a coupled process involving Pauson-Khand and Michael-type reactions. The formation of cyclopentenone derivatives is strongly dependent on the nature of the alkyne and of the activated alkene.

The synthesis of cyclopentenone derivatives by cocyclization of alkynes with alkenes and carbon monoxide in the presence of cobalt carbonyl complexes (known as the Pauson-Khand reaction PKR) has become a synthetically important reaction.[1] Most noticeably, however, the reaction fails to yield cyclopentenone derivatives with alkenes bearing electron-withdrawing groups (EWG).[2] Instead of giving cyclopentenones through a formal 2+2+1 cycloaddition process, the π-conjugated EWG on the alkene apparently makes a β-hydrogen elimination step leading to a diene product competitive with CO insertion. Scheme 1.

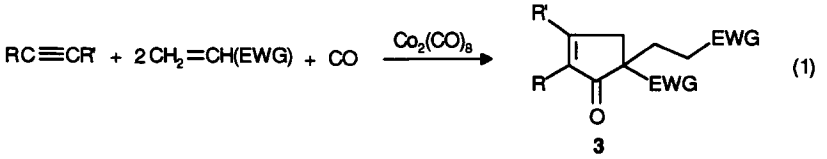



R, R' = H, alkyl, aryl; EWG = CHO, $CO_2$Alk, CN

**Scheme 1**

Styrene derivatives show an intermediate behaviour giving comparable yields of dienes and 5-arylcyclopentenones both with complete regioselectivity.[3] Two examples of stoichiometric intramolecular cyclization of 1,6-enyne bearing EWG were recently reported.[4]

We now have found that in the presence of an excess of $CH_2$=CH(EWG) (EWG = $CO_2$Alk, CN) the PKR can be driven towards substituted cyclopentenone formation by addition of a second $CH_2$=CH(EWG) molecule in an one-pot reaction according to eqn. 1.

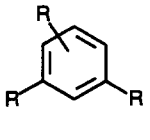



(1)

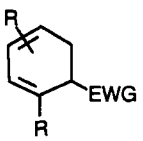
Thus 1-hexyne (11.3 mmol) reacted with an excess of methyl acrylate (20 ml) and carbon monoxide (40 bar) at 120° C in autoclave for 32h in the presence of $Co_2(CO)_8$ (0.54 mmol) as catalyst giving cyclopentenone **3** (R = nBu, R' = H, EWG = $CO_2Me$) (44%)[5] along with a small amount (5%) of 2-norbornanones, (mixture of two stereoisomers ca. 1:1.5) not yet identified unequivocally, derived by further ring closure via intramolecular Michael-type reaction of the substituted cyclopentenone. It is noteworthy that adding a base such as 2,6-di*tert*-butyl-4-methylpyridine (0.25g 1.2mmol) caused the yield of **3** to increase to 53%[5] along with 7% of 2-norbonananones (two stereoisomers as reported above) Symmetrically and unsymmetrycally-substituted benzenes (**4**, R = nBu) in ca. 1:1 ratio were formed to the extent of 4% by cyclotrimerization of the alkyne.[6] Methyl 2,4 and 2,5-dibutyl-2,4-cyclohexadiene carboxylates (**5**, R = nBu) (from cyclocotrimerization of two molecules of alkynes with one of the olefin)[6] accounted for another 5% (ca. 1:1 ratio); finally two stereoisomers of the acyclic diene **2**(probably *trans, trans* and *cis, trans*) corresponding to the product obtained by Pauson-Khand[2,3] from the condensation of a molecule of 1-hexyne with one of methyl acrylate were present in 3% yield (ca. 2:1 ratio). Other heavy products could not be isolated.

The formation of the cyclopentenone derivative **3** is favoured by decreasing the concentration of the alkyne (ca. 0.56 mol/l), increasing CO pressure (40 bar) and using a large excess of the activated olefin, preferably used as solvent. Using a 1:1 mixture of toluene and methyl acrylate as solvent with 1-hexyne lowered the yield of **3** to 29%. Under the same conditions the reaction of acrylic esters, used as solvent, with other alkynes such as phenylacetylene, *tert*-butylacetylene and trimethylsilylacetylene gave 29, 24 and 8% yield, respectively, of product **3** (R = Ph, R' = H, EWG = $CO_2Et$; R = $Me_3C$, $Me_3Si$, R' = H, EWG = $CO_2Me$).

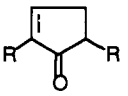
The structure of the alkyne affects chemoselectivity remarkably. Thus with phenylacetylene the yields of the phenyl-substituted compounds corresponding to **4** and **5** (R = Ph, EWG = $CO_2Et$) were 30 and 25%, respectively, while with trimethylsilylacetylene a 50% yield of **5** (R = $Me_3Si$, EWG = $CO_2Me$) was obtained along with 8% of a cyclopentenone derivative **6** (semihydrogenated cyclopentadienone from two alkyne and one CO molecules) and with *tert*-butylacetylene products **7** and **8** (R = $Me_3C$, EWG = $CO_2Me$) were formed in 3 and 35% yield, respectively.[6,7]



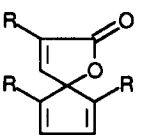

**4**



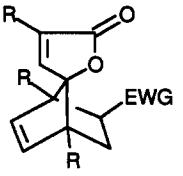

**5**




**6**




**7**



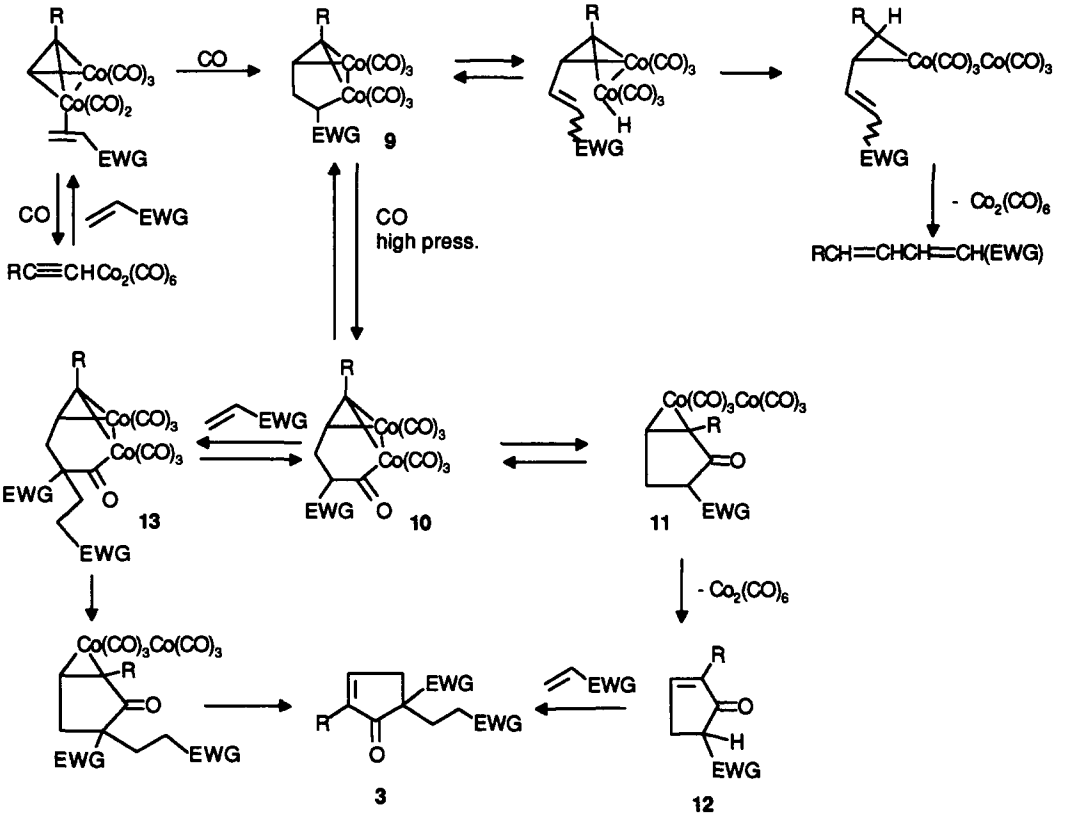

**8**

Terminal alkynes gave much better yields of cyclopentenones **3** than the internal ones, which gave yields below 15%.

The nature of the alkenes influences the course of the reaction too. The reaction of 1-hexyne (5.65 mmol) with ethyl acrylate or acrylonitrile as solvent (6 ml) under the same conditions leading to 44% yield with methyl acrylate yielded 42 and 24%, respectively, of product **3** (R = nBu, R' = H, EWG = $CO_2Et$, CN). The reaction failed both with 1,1-disubstituted alkenes such as methyl crotonate and 1,1-disubstituted alkenes such as methyl methacrylate.

The reaction leading to **3** is regioselactive both with respect to the alkyne and to the alkene, the coupling of C-C atoms occurring at the less hindered sites. We interpret the initial steps of the reaction as involving cobaltacycle intermediates according to the Pauson-Khand mechanism.[1] The dinuclear cobaltacycle **9**, represented in Scheme 2, reversibly inserts carbon monoxide (in competition with β–hydrogen elimination) to give complex **10.** At this point the latter could undergo a Michael-type reaction[8] with the olefin at the active

CH site, thus driving the preceding steps towards the otherwise unfavourable formation of the cyclopentenone ring. It has not yet been ascertained, however, whether the intervention of the second (EWG)CH=$CH_2$ molecule occurs on cobaltacycle (**10**) or on the free (**12**) or cobalt-bonded disubstituted cyclopentenone (**11**) (so far not detected) which must be in equilibrium with **10**. An attempt to obtain **12** from **3** by a reverse Michael-type reaction at 140°C for 24h in the presence of a base and $Co_2(CO)_8$ failed. This suggests that the reaction could proceed through intermediate **13**.




**Scheme 2**

**Acknowledgments.** We thank CNR and MURST for financial support, and Centro Interfacoltà di Misure of the University of Parma for NMR and mass spectroscopy facilities.

**References and Notes**

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5 Yields, based on starting alkynes, are for isolated compounds (chromatography on $SiO_2$); all new compounds were fully characterised by $^1H$, $^{13}C$ and homonuclear $^1H$ 2D-COSY NMR experiments, IR, mass spectroscopy and elemental analysis. Spectroscopic data of selected products: **3** (R = nBu, R' = H, EWG = $CO_2Me$, pale yellow oil): MS (EI, 70eV): m/z = 282 ($M^+$, 6%), 251 (48), 250 (53), 222 (33), 190 (100), 163 (38), 162 (44), 149 (9), 148 (14), 147 (10), 121 (14), 120 (10), 119 (32), 107 (9), 91 (29), 79 (23), 77 (24), 59 (29), 55 (94) and 41 (30). FTIR (film) $1/\nu$ [$cm^{-1}$] = 2956 (s), 2912(s), 2873 (m), 1740 (s), 1705 (s), 1636 (m), 1437 (s), 1377 (m), 1256 (s), 1197 (s), 1162 (s), 1085 (w), 1018 (w) and 847 (w). $^1H$-NMR (400 Mhz, $CDCl_3$): $\delta$ [ppm] = 0.87 (t, 3H, J = 7.3 Hz, $CH_2CH_3$), 1.24-1.33 (m, 2H, $CH_2Me$), 1.39-1.47 (m, 2H, $CH_2Et$), 2.03-2.09 (m, 1H, $CHHCH_2CO_2Me$), 2.12-2.17 (m, 2H, $nPrCH_2C$=), 2.20-2.25 (m, 2H, $CH_2CO_2Me$), 2.32-2.37 (m, 1H, $CHHCH_2CO_2Me$), 2.44 (ddt, 1H, J = 18.8/ 2.8/ 1.9 Hz, $CHHCH$=), 3.06 (ddt, 1H, J = 18.8/ 2.8/ 1.9 Hz, $CHHCH$=), 3.62 (s, 3H, $OCH_3$), 3.65 (s, 3H, $OCH_3$) and 7.29-7.31 (m,septet, 1H, =CH). $^{13}C$-NMR (75 Mhz, $CDCl_3$): $\delta$ [ppm] = 13.56 ($CH_3$), 22.10 ($CH_2$), 24.37 ($CH_2$), 29.15 (br s $2CH_2$), 29.40 ($CH_2$), 37.46 ($CH_2$), 51.42 ($OCH_3$), 52.38 ($OCH_3$), 56.95 (q C), 144.27 (q. C), 155.85 (=CH), 170.90 (CO), 172.94 (CO) and 204.48 (CO).

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