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Group VI Metal-Promoted *Endo*-Carbocyclizations via Alkyne-Derived Metal Vinylidene Carbenes

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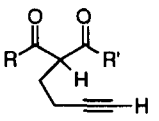
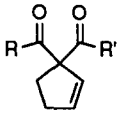
Abstract: The molybdenum-promoted cycloisomerization of terminal alkynes tethered to β-dicarbonyl nucleophiles is described, providing a novel synthesis of 1,1-disubstituted-2-cyclopentenes.

Our laboratory has been engaged in a program of cyclic ether synthesis via intramolecular addition of alcohol nucleophiles into vinylidene metal carbenes (produced by *in situ* rearrangement of terminal alkynes), which affords the cycloisomeric endocyclic enol ethers.[1] We anticipated that this terminal alkyne / vinylidene cyclization concept might be extended to a novel carbocycloisomerization transformation with carbon nucleophiles such as stabilized carbanions, despite the absence of precedents for such a reaction.[2]

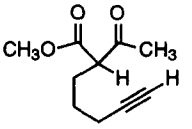
We found that reaction of a diethyl ether solution of (3-butyn-1-yl)malonate **1** with a strong base (sodium hydride or sodium methoxide) followed by addition of this stabilized enolate solution to $(Et_3N)Mo(CO)_5$ afforded the isomeric cyclopentene **4** (Table 1).[3,4] Further studies showed that cycloisomerization occurred even with substoichiometric amounts of sodium hydride and $(Et_3N)Mo(CO)_5$, and best yields of cyclopentene **4** were generally obtained by using 25 - 50 mol% of both the base and the molybdenum reagent. Similar procedures promoted the cycloisomerization of the more acidic ketoester and diketone-tethered alkynes **2** and **3**. However, homologous substrates including **7** were recovered unchanged unless the reaction mixture was heated to reflux, which then resulted in production of the exocyclic alkene **8** rather than the endocyclic cyclohexene products.[5]



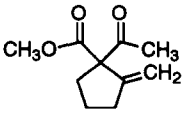
1 R = R' = OCH_3
2 R = OCH_3, R' = CH_3
3 R = R' = CH_3



4 R = R' = OCH_3
5 R = OCH_3, R' = CH_3
6 R = R' = CH_3



7



8

substrate	conditions	product (isolated yield)
1	NaH (0.5 equiv), Et_2O; then $(Et_3N)Mo(CO)_5$ (0.5 equiv), 20°C, 24 h	**4** (60%)
2	NaH (0.5 equiv), Et_2O; then $(Et_3N)Mo(CO)_5$ (0.5 equiv), 20°C, 24 h	**5** (42%)
3	NaH (0.5 equiv), Et_2O; then $(Et_3N)Mo(CO)_5$ (0.5 equiv), 20°C, 24 h	**6** (57%)
7	NaH (0.5 equiv), Et_2O; then $(Et_3N)Mo(CO)_5$ (0.5 equiv), 35°C, 72 h	**8** (62%)

These examples of the *endo*-carbocyclization reaction represent a novel yet conceptually simple cyclization transformation which affords cyclopentene products which were previously unknown in the literature.[6] Additional examples of similar carbocyclization transformations as well as mechanistic studies are in progress.

Representative procedure for carbocyclization: $Mo(CO)_6$ (132 mg, 0.5 mmol) was placed into a dry 18 x 150 mm test tube and purged with nitrogen. Ether (12 mL) and freshly distilled triethylamine (4 mL) were added, the solution was stirred to dissolution, and the test tube was photolyzed under nitrogen for 20 min. The resulting yellow solution of $(Et_3N)Mo(CO)_5$ was immediately used in the next step. In a separate flask, sodium hydride (60% in mineral oil, 20 mg, 0.5 mmol) was placed into a dry roundbottom flask and purged with nitrogen. Ether (10 mL) was added followed by dropwise addition of the appropriate alkyne substrate **1** - **3** (1.0 mmol). The freshly prepared solution of $(Et_3N)Mo(CO)_5$ was then added and the mixture was stirred under nitrogen at 20°C. After reaction was judged complete by TLC analysis, solvent was evaporated, and the residue was purified by flash chromatography to provide products **4** - **6**.

1,1-Bis(carbomethoxy)-2-cyclopentene (**4**): IR (neat) 3283, 2954, 1734, 1435, 1262, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.02-6.00 (1H, m), 5.83-5.81 (1H, m), 3.73 (6H, s), 2.50-2.44 (4H, m); ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.7, 135.9, 128.6, 69.0, 52.7, 31.9, 31.6; MS (70eV, LREI) 184, 152, 145, 125, 93, 59; HRMS calcd for $C_9H_{12}O_4$ (M^+) 184.074, found 184.073; Anal. calcd C, 58.69; H, 6.57; found C, 59.06; H, 6.51.

1-(Acetyl)-1-(carbomethoxy)-2-cyclopentene (**5**): IR (neat) 2927, 1743, 1714, 1434, 1357, 1254, 1075 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (1H, dd, J = 5.6, 2.3 Hz), 5.87 (1H, dd, J = 5.6, 2.1 Hz), 3.74 (3H, s), 2.53-2.35 (4H, m), 2.18 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 203.8, 172.3, 136.4, 128.6, 73.5, 52.6, 31.9, 30.1, 26.4; MS (70eV, LREI) 126, 111, 94, 67, 43; HRMS calcd for $C_7H_{10}O_2$ (M - CH_3CO + H^+) 126.0681, found 126.0702; Anal. calcd C, 64.27; H, 7.19; found C, 63.97; H, 7.39.

1,1-Bis(acetyl)-2-cyclopentene (**6**): IR (neat) 3279, 2928, 1699, 1612, 1424, 1357, 1206, 1151, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.05 (1H, dt, J = 5.7, 2.3 Hz), 5.96 (1H, dt, J = 5.7, 2.1 Hz), 2.52-2.43 (2H, m), 2.39-2.33 (2H, m), 2.14 (6H, s); ^{13}C NMR (300 MHz, $CDCl_3$) δ 205.6, 136.9, 128.6, 69.0, 31.9, 28.9, 26.9; MS (70eV, LREI) 152, 126, 113, 110, 71, 43; HRMS calcd for $C_9H_{12}O_2$ (M^+) 152.084, found 152.082; Anal. calcd C, 71.03; H, 7.95; found C, 70.90; H, 7.82.

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References and Notes

1. McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648, and references therein.
2. Ruthenium-catalyzed cycloisomerization of alkynyldienes to benzenoid compounds was recently reported: Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319.
3. Compounds **1** - **3** were prepared by enolization and alkylation of the simple β-dicarbonyl compound with 4-iodo-1-butyne: (a) Taylor, E. C.; Macor, J. E.; French, L. G. *J. Org. Chem.* **1991**, *56*, 1807. (b) Eglington, G.; Whiting, M. C. *J. Chem. Soc.* **1950**, 3653. (c) Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1991**, *47*, 6293.
4. Substrate **1** was recovered unchanged upon simply mixing with $(Et_3N)Mo(CO)_5$ in diethyl ether, therefore the initial deprotonation step is essential for successful cyclization. Reaction of **1** with sodium hydride followed by addition to either $Cr(CO)_6$ / trimethylamine *N*-oxide, or $(THF)W(CO)_5$ also produced cyclopentene **4**, but in considerably lower isolated yields.
5. Other Lewis acidic metal reagents also promote *exo*-carbocyclizations: (a) Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801. (b) Forsyth, C. J.; Clardy, J. *J. Am. Chem. Soc.* **1990**, *112*, 3497. (c) Monteiro, N.; Gore, J.; Balme, G. *Tetrahedron* **1992**, *48*, 10103. (d) Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699.
6. (a) Compound **4** is mentioned once in the literature, produced in very low yield as a component of an inseparable mixture with the 3-cyclopentene isomer: Abram, T. S.; Baker, R.; Exon, C.; Rao, V. B. *J. Chem. Soc., Perkin Trans 1* **1982**, 285.

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